UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., Plaintiffs, -v- MYLAN LABORATORIES, INC., MYLAN PHARMACEUTICALS, INC., and UDL LABORATORIES, INC., Defendants.	03 CIV. 8253 (DLC)
	OPINION & ORDER
TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., Plaintiffs, -v- ALPHAPHARM PTY. LTD. and GENPHARM, INC., Defendants.	04 CIV. 1966 (DLC)

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DENISE COTE, District Judge:

Takeda Pharmaceutical Company Limited ("Takeda") and Takeda Pharmaceuticals North America, Inc. ("Takeda North America") have brought this patent action under the Food Drug Cosmetic Act, 21 U.S.C. §§ 301-99, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub L. No. 98-417, 98 Stat. 1585 (1984) (codified in scattered sections of titles 21, 35, and 42 U.S.C.) (the "Hatch-Waxman Act"), and under the patent laws of the United States, alleging that four generic drug manufacturers have infringed and will induce infringement of Takeda's patents protecting its product ACTOS®, a drug used to treat Type 2 diabetes.

This Opinion presents the findings of fact and conclusions of law following a bench trial held between January 17 and January 30, 2006, to resolve the challenges made by defendants to Takeda's U.S. Patent No. 4,687,777 ("'777 Patent"), which protects the invention of the chemical compound 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione ("pioglitazone"). Alphapharm Pty. Ltd. and Genpharm, Inc. ("Alphapharm") contend that the invention is obvious based on the disclosure by Takeda

of a structurally similar molecule in the prior art. Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. ("Mylan") contend that Takeda deceived the Patent and Trademark Office ("PTO") when it applied for the '777 Patent, principally by misrepresenting the results of efficacy and toxicity tests. Neither challenge is meritorious. The length of this Opinion is occasioned by the need to address the many iterations of the defendants' arguments, as they searched for a viable theory to attack the '777 Patent.

As described below, the '777 Patent discloses a remarkable invention. After decades of work to develop an anti-diabetic treatment, Takeda discovered a pharmaceutical agent that was both effective and non-toxic. This represented a significant advance over compounds disclosed in the prior art. Takeda's application to the PTO for the '777 Patent reported the very analysis of test results on which Takeda itself had previously relied to select the pioglitazone molecule from the thousands it had synthesized and the hundreds it had tested. Faced with the task of proving their cases by clear and convincing evidence, both Alphapharm and Mylan have failed to make even a rudimentary showing that the invention was obvious or that Takeda engaged in inequitable conduct. Their challenges to the '777 Patent are rejected.

Trial Procedure

The trial was conducted in accordance with the Court's Individual Practices and the Scheduling Order dated July 20,

2004. The parties filed a Joint Pretrial Order and accompanying memoranda of law and proposed findings of fact and conclusions of law on November 18, 2005. The parties also served affidavits containing the direct testimony of all their witnesses, as well as copies of all the exhibits and deposition testimony which they intended to offer as evidence in chief at trial.

A science tutorial was held on December 1, 2005. Testifying for Takeda were Silvio Inzucchi ("Inzucchi"), a Professor of Medicine at Yale University and expert endocrinologist who serves as the Director of the Yale Diabetes Center; James Hendrickson ("Hendrickson"), the Henry F. Fischbach Professor of Chemistry, retired, at Brandeis University and an expert in organic chemistry; and Peter Valberg, a senior scientist at a private environmental health consulting firm, an expert in the statistical analysis of animal testing data, and formerly an Associate Professor of Physiology at Harvard's School of Public Health. Testifying for Alphapharm was Henry Mosberg ("Mosberg"), a Professor of Medicinal Chemistry at the University of Michigan, and an expert in drug design. Testifying for Mylan was Lawrence Hendry ("Hendry"), an Adjunct Professor of Physiology and Endocrinology at the Medical College of Georgia, an Associate Adjunct Professor of Medicinal Chemistry at the University of Georgia, and the founder of a chemical design firm.

The plaintiffs and defendants were each given twenty-four hours for opening statements, examination of witnesses and evidentiary arguments at trial. Of the time granted the

defendants, Alphapharm was given eight hours and Mylan sixteen hours.[1] The parties were given additional time for summations.

In addition to the experts who testified on December 1, the following witnesses testified at trial. For Takeda, Richard Daly, Senior Vice President of Marketing at Takeda North America; William Kettyle ("Kettyle"), an expert endocrinologist with significant expertise in the treatment of diabetes; Loren Koller ("Koller"), a doctor in veterinary medicine, an environmental health and toxicology consultant, an expert in immunotoxicology, and an officer of the Association for Assessment and Accreditation of Laboratory Animal Care International; Takeshi Fujita ("Fujita"), a former Takeda employee who, as the Chief Scientist of Takeda's Biology Research Laboratory, was the co-inventor on the '777 Patent; Samuel Danishefsky ("Danishefsky"), a Professor of Chemistry at Columbia University who holds the Kettering Chair at the Memorial Sloan-Kettering Cancer Institute; Yasuo Sugiyama, Takeda's Manager of Strategic Research Planning and a researcher who was involved in the development of pioglitazone; Bernard Landau ("Landau"), a Professor of Biochemistry at Case and Western Reserve University, and, in 1996, a Nobel Fellow at the Karolinska Institute in Sweden; Bruce Stoner ("Stoner"), a former Chief Administrative Patent Judge; Gerard Colca ("Colca"), a former senior research scientist in metabolic disease research at The Upjohn Company ("Upjohn"), a

[1] When the defendants exhausted their time at trial, they were given a limited amount of additional time.

U.S. pharmaceutical company that had worked with Takeda in the development of pioglitazone; and Douglas Morton, a former Director of Diabetes and Gastrointestinal Diseases Research at Upjohn.

Testifying for Alphapharm was Richard Wright, a Professor of Economics at the University of California at Berkeley, and a member of the Steering Committee for Berkeley's Center for Hunger and Obesity. Testifying for Mylan was Martin Ronis ("Ronis"), a Professor of Medicinal Sciences at the University of Arkansas, Associate Director of the Arkansas Childrens' Nutrition Center and an expert in chemical testing in animals. Mylan also presented the declaration of Mark Nusbaum ("Nusbaum"), a former Examiner-in-Chief and member of the Board of Patent Appeal and Interferences.[2]

The parties also offered excerpts from the deposition testimony of some of the fact witnesses that testified at trial and of the following individuals: Michael Davis, the American patent attorney who prosecuted the '777 Patent; Yoshikazu Hasagawa, the Senior Manager in charge of Intellectual Property litigation for Takeda; Shelly Monteleone, Intellectual Property Counsel for Mylan; Brett Mooney, an Alphapharm employee involved in pharmaceutical development; Hiroyuki Odaka, a former Takeda employee who worked in Takeda's Biology Research Laboratories at the time of the development of pioglitazone; Brian Roman, an

[2] Takeda chose not to cross-examine Nusbaum and thus he did not appear at trial.

attorney and a Rule 30(b)(6) witness for Mylan; Howard Rosenberg ("Rosenberg"), the Group Intellectual Property and API Strategy Director for Generics U.K., a sister company of Alphapharm, and an Alphapharm Rule 30(b)(6) witness; Michael Rosenberg, the owner of Health Decisions, a company engaged in clinical research; Takashi Sohda, General Manager of Takeda's Pharmaceutical Research Division; Barry Spencer, a Senior Patent Officer at Alphapharm and a Rule 30(b)(6) witness for Alphapharm; Shigehisa Taketomi, a Takeda employee and Rule 30(b)(6) witness for Takeda; and Stephen Talton, a Mylan employee responsible for preparing applications to sell generic drugs.

The findings of fact based on the evidence presented at trial are scattered throughout this Opinion. The background section contains the story of the development of pioglitazone, an introduction to the prior art, a description of the relevant patents and their file histories, an introduction to the science that is necessary to understand the discussion that follows, and an outline of the procedural history of this litigation. The discussion section of the Opinion will address first the issue of obviousness and then the issue of inequitable conduct.

Background

A. Diabetes

Diabetes is a disease in which the body is unable to metabolize blood sugar or glucose derived from food, primarily carbohydrates, into energy efficiently. The blood glucose level

is essentially controlled by insulin, which drives the process whereby glucose enters the cells of the body and is turned into energy. Insulin is a hormone made by specialized cells within the pancreas called beta cells.

There are two types of diabetes. Type 1 diabetes is characterized by the fact that the pancreas does not produce insulin. Insulin must therefore be supplied from an external source, such as an injection or insulin pump. Type 1 diabetes compromises less than 10% of diabetes cases worldwide.

In Type 2 diabetes, the body fails to utilize effectively the insulin that is produced. This failure usually starts in the muscles, which collectively use most of the glucose produced by the body. The liver is also responsive to insulin, which instructs the liver when to stop making glucose. When the liver becomes insulin resistant, it resists those instructions and continues to create glucose. Insulin resistance also impacts the pancreas, at first by forcing it to produce more insulin than normal. Over time, the increased resistance to the action of insulin overwhelms the ability of the pancreas to produce sufficient insulin, and the symptoms of diabetes begin to appear. If Type 2 diabetes is left untreated, the demand for insulin from the pancreas can eventually lead the beta cells to become dysfunctional, a phenomenon known as “exhaustion” or “burn-out.”

Diabetes can cause great damage to the body. Due to the toxic effects of high glucose on blood vessels, patients with diabetes are predisposed to chronic complications such as kidney

failure, blindness, leg ulcers and amputations, heart attacks, and strokes.

B. Treatments of Diabetes

Type 2 diabetes may be treated with lifestyle changes, such as weight loss, improved diet, and exercise. These steps are rarely sufficient. A substantial portion of patients ultimately need injections of insulin. Insulin is effective because insulin resistence in Type 2 patients is not complete -- insulin may still lower blood glucose.

The past twenty-five years have seen the development of a number of oral antidiabetic drugs ("OAD") that are used instead of, or in conjunction with, insulin. Different classes of OADs have that have been developed work in the different parts of the body affected by diabetes. It is common practice to treat diabetes with a combination of several classes of drugs.

Sulphonylureas, which became available in the 1980s, are the oldest class of drug used to treat Type 2 diabetes, and work by stimulating the pancreas to secrete more insulin. Meglitinides work very much like the sulphonylureas but differ in that their onset is more rapid and their duration of action is briefer.[3] Biguanides help to reduce the liver's production of glucose. Metformin®, a biguanide, is frequently the first drug chosen to treat a newly diagnosed Type 2 diabetes patient. It became

[3] Alpha-glucosidase inhibitors, which are used infrequently in the United States, interfere with starch absorption in the intestine, thereby slowing the increase in blood glucose levels after meals.

available in 1995.

The treatment of diabetes was revolutionized in the 1990's with the introduction of a class of drugs known as thiazolidinediones (“TZDs”). TZDs were first discovered by Takeda in the 1970s. They are peripheral insulin sensitizers, working within muscles to enhance the effect of insulin in that organ, and thereby to increase the muscles’ ability to take glucose from the bloodstream.

The first TZD to be marketed in the United States was troglitazone, known by the commercial name Rezulin®. Rezulin®, which was developed by Pfizer, first became available in 1997. In May of 1999, two years after Rezulin® entered on the market, the Food and Drug Administration (“FDA”) approved GlaxoSmithKline’s Avandia® (whose active ingredient is rosiglitazone). The drug at issue here, ACTOS®, which was approved by the FDA in July of 1999, is the only other TZD currently approved by the FDA for sale in the United States.

In March 2000, Pfizer withdrew Rezulin® from the United States market due to significant concerns about its safety. After Rezulin® was withdrawn, ACTOS® and Avandia® essentially split the TZD market in the United States. More recently, research has shown that these two TZDs have a greater positive effect in the treatment of cardiovascular disease than other anti-diabetic drugs, and that ACTOS® in particular has a greater

impact than Avandia® on lowering cardiovascular risk.[4] Based in part on this research, there is evidence that ACTOS® is becoming the preferred TZD among knowledgeable doctors.

By any measure, ACTOS® has been a hugely successful commercial product. It has led the TZD market for new prescriptions written by endocrinologists since February 25, 2000. In October 2001, it became the seventh fastest product in pharmaceutical history to reach $1 billion in annual sales.

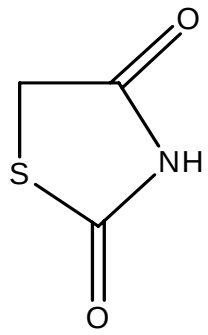
C. Takeda's Research into Diabetes

Takeda, a Japanese pharmaceutical company, is based in Osaka, Japan. Takeda North America is a wholly owned United States subsidiary of Takeda America Holdings, Inc., which is a wholly owned subsidiary of Takeda.

Takeda began its research into obesity and related diseases in the early 1960s. Working with Nagoya University in Japan, Takeda developed an animal model that exhibits the symptoms of diabetes: KKA^{y} mice. This is an obese strain of mice that consistently exhibits symptoms of insulin resistance under normal diet conditions. Takeda researchers also developed the genetically obese and diabetic Wistar fatty rat. The development of the KKA^{y} mouse and the Wistar fatty rat were significant steps in the effort to develop pharmaceutical treatments for diabetes since compounds could now be tested in diabetic animals.

[4] To reduce cardiovascular risk both trigylcerides and LDL-cholesterol should be lowered. Pioglitazone has shown better trigylceride lowering properties than rosiglitazone and also has shown less of an effect of raising LDL-cholesterol.

Takeda made a pharmacological breakthrough in the 1970s. Takeda researchers discovered the first TZD derivative compound and learned that TZDs exhibited considerable blood glucose lowering effects in KKA^{y} mice.[5] The defining characteristic of TZDs is the presence of a thiazolidinedione group at the right end or moeity[6] of a molecule. The chemical structure of this group is:



Takeda's work with TZD derivatives revealed that at least some compounds within the TZD class did not lower blood glucose in normal, non-diabetic animals. This was another important finding because it suggested that TZD derivatives did not affect the level of insulin in the body, but instead were insulin sensitizers, a term for compounds that ameliorate insulin resistance, the defining characteristic of Type 2 diabetes.

While scientists did not initially understand how TZDs work,

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[5] Takeda's diabetes research was conducted through a partnership of Dr. Yutaka Kawamatsu, who ran the chemical research into TZDs and Fujita, who oversaw the biological research.

[6] A moiety is a "group of atoms forming a distinct part of a large molecule." Oxford English Dictionary (Draft Revision to 2d Ed. December 2003).

and still debate today precisely how TZDs actually function within the body, there is a growing consensus that TZDs enhance the signal of insulin receptors that reside in the cells that require or store energy, such as muscles and fat cells. When we eat, the level of glucose rises in the bloodstream, stimulating the pancreas to secrete more insulin. The insulin which is flowing through the blood binds to insulin receptors, causing changes inside cells that allow glucose to enter the cell from the bloodstream, where it can be burned for energy or stored. Because of a negative feedback system, as the level of glucose in the blood falls, the pancreas produces less insulin so that the blood glucose returns to normal levels.

TZDs activate the insulin receptors by binding to a molecule within the cell's nucleus known as PPAR-gamma. Together, they bind to specific areas on the cell's DNA, producing messenger RNA and effectively stimulating the production of glucose transporters within the cell. The transporters travel to the surface of the cell and facilitate the entry of glucose into the cell from the bloodstream.

Scientists still do not fully understand how insulin resistance works at the cellular level, but it is believed that the problem relates to the interaction between the insulin receptors and that section of the DNA in the cell's nucleus that is responsible for triggering the production of glucose transporters. As noted, TZDs work by binding with a molecule in the nucleus of the cell called PPAR-gamma. When that happens,

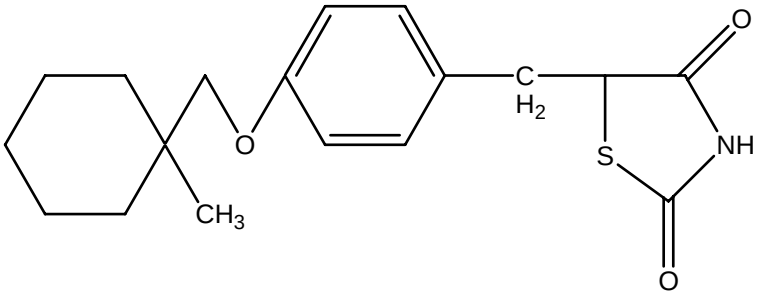
the PPAR-gamma molecule changes shape and binds to the DNA in the cell. Each TZD seems to bind differently with the PPAR-gamma. As a result, different TZDs have different metabolic effects. TZDs also bind with other PPAR molecules in the cell, such as the PPAR-alpha and PPAR-delta molecules, further contributing to the differences among TZDs.

The fact that TZDs affect the gene transcription process within DNA makes them both effective but also unpredictable. Only a fraction of the genes in the human body have been identified. It is possible that TZDs stimulate genes that are still unknown. As one of Takeda's expert endocrinologists has explained, gene transcription is "a big black box.... When you are stimulating a gene, you can do a lot of things downstream that you may not understand."

D. The Development of Ciglitazone and the '200 Patent

Takeda's research led to the synthesis of the TZD ciglitazone in February of 1978. Takeda worked for many years to develop ciglitazone, only abandoning it when it proved toxic during human clinical trials. Thereafter, Takeda's search for a TZD to develop as a commercial pharmaceutical used ciglitazone as a benchmark. Takeda searched for a compound that was more potent than ciglitazone, which required unrealistically high doses to be effective, and yet non-toxic.

Ciglitazone's chemical structure is illustrated here:



Ciglitazone

It was identified as a particularly promising compound based on its blood lowering effect in KKA^{y} mice. Based on this research, Takeda filed a United States patent application on July 27, 1979, covering a generic class of TZD derivatives including ciglitazone. The application eventually resulted in the issuance of U.S. Patent No. 4,287,200 ("'200 Patent").

The application for the '200 Patent ("'200 Application") made eight claims. Its first claim was its broadest and covered hundreds of millions of TZD compounds through a formula that allowed for a wide variety of chemical structures on the left-hand end to be attached to the TZD structure on the right. The '200 Application represented that TZDs are "novel compounds and useful as, for example, remedies for diabetes, hyperlipemia and so on of mammals including human beings."

The '200 Application was the subject of two office actions by the PTO. The second office action allowed two of the eight claims, but rejected all of the other claims as containing "improper Markush groups." See Ex parte Markush, 1925 CD 126,

340 Off. Gaz. Pat. Office 839 (Comm'r. Pat. 1925).[7] The office action identified three separate groups the patent examiner believed were contained in the '200 Application.[8]

In response to the second office action, Takeda amended its application to cover only the first of the three groups identified by the examiner. In the amendment Takeda noted that it might file "divisional applications" to cover the other groups.

The '200 Patent was issued on September 1, 1981. Fujita and Dr. Yutaka Kawamatsu were named as co-inventors. In addition to the generic class of TZDs, the patent also presented, as examples, sixty specific compounds covered by the generic formula. Included among those disclosed was compound 42, whose left end was a 2-pyridyl ring with a methyl at the 6-position. Compound 42 is a compound of importance to this litigation and is discussed in detail below.[9] Like ciglitazone, compound 42 had

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[7] The examiner cited a recent appellate decision, In re Harnisch, 631 F.2d 716 (C.C.P.A. 1980), as providing a legal basis for the rejection. Harnisch confirmed the concept of an "improper Markush group" as a basis for rejecting a patent application. Id. at 721. The decision explained that the issue underlying improper "Markush groups" was better described as a lack of "unity of invention." Id.

[8] The three groups identified were distinguished by the possible structures on the left end moiety. Group A was composed of compounds where the left end moiety contained an alkyl, cycloalkyl or phenylalkyl; for Group B the left end contained a thienyl or furyl; for Group C the left end contained a pyridyl or thiazolyl. It is this last group that is of importance here; pioglitazone is a left end pyridyl.

[9] Compound 42 from the '200 Patent is compound (b) from the '777 Patent.

first been synthesized in 1978.

E. Two Divisional Patents

Takeda obtained two divisional patents for the ‘200 Patent. First, through a patent issued on July 20, 1982, as U.S. Patent No. 4,340,605 (“‘605 Patent”), Takeda received a patent for the third group identified by the examiner.[10] In support of the application for that patent, Takeda presented a declaration from Fujita providing data for blood glucose and lipid lowering effects of twelve compounds tested in KKA^{Y} Mice, including compound 42 from the ‘200 Application.

On July 7, 1982, Takeda filed an application for a second divisional to the ‘200 Patent. The patent, which issued on March 20, 1984, as U.S. Patent 4,438,141 (“‘141 Patent”), covered the second grouping that was identified by the examiner in the course of prosecuting the ‘200 Patent.

F. Sohda II

While it was securing the ‘200 Patent, Takeda continued its research into TZD derivatives and by early 1982 had evaluated approximately 1000 compounds for their potential as antidiabetic agents. Important information about TZDs and Takeda’s research efforts was published in a series of articles by Takeda’s scientists. Of particular importance to this Opinion, because it constitutes prior art for the ‘777 Patent, was an article

[10] The third group identified, compounds with a pyridyl or thiazoyl on the left end, had been designated group C by the examiner.

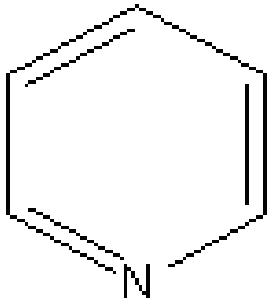
received for publication on April 22, 1982, T. Sohda et al., Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]) thiazolidine-2,4-dione (ADD-3878) and its Derivatives, Chem. Pharm. Bull., 30:3580-3600 (1982) ("Sohda II"). Sohda II did not disclose pioglitazone, but it did disclose a compound that was structurally close to pioglitazone, and which Alphapharm contends made the invention of pioglitazone obvious.

Sohda II described 101 specific TZD compounds, giving data on each compound's efficacy. As was the case in the Fujita declaration submitted in the prosecution of the '605 Patent, the data were presented as a score ranging from one to four in two categories: hypoglycemic activity (blood sugar lowering activity) and plasma triglyceride lowering activity. A higher score represented greater potency.

While the article did not present data on the toxicity or side effects of the compounds, it did comment on these issues for particular compounds. Of the 101 compounds, the article identified three compounds -- compounds 47, 49 and 59 -- as showing the most favorable profiles "in terms of activity and toxicity." The article concluded that those three compounds "may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity." Compound 49 was ciglitazone and compound 47 was a compound whose left end was structurally similar to ciglitazone's. The left end of compound 59 was different from 47 and 49, its left end terminated with a

3-pyridyl ring.

Since pioglitazone has a pyridyl ring at its left end, it is important to discuss compound 59 and related compounds described in Sohda II in some detail. To begin with, the term pyridine refers to a six-membered carbon-containing ring with one carbon replaced by a nitrogen. A pyridyl ring is diagramed as follows:

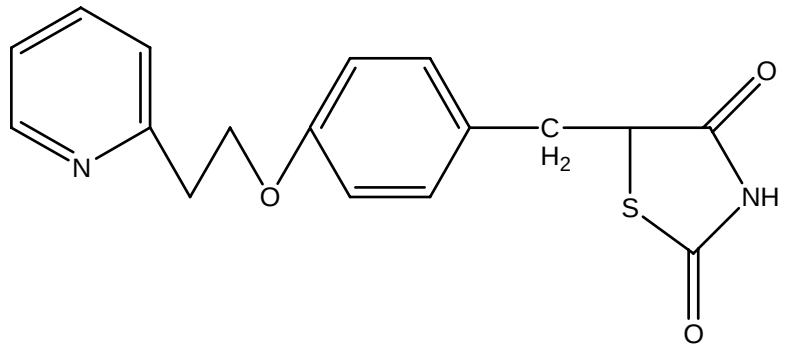


Pyridine

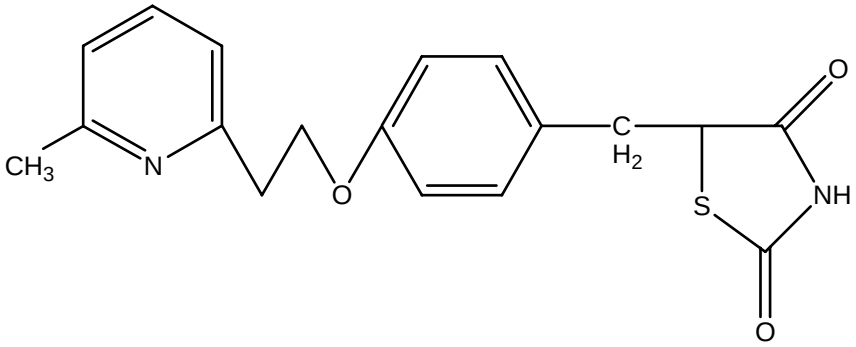
The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion. As noted, compound 59 was a 3-pyridyl ring, which means that the ring is attached at the third position to the rest of the molecule.

The article disclosed two 2-pyridyl compounds: compound 57, the unsubstituted 2-pyridyl, and compound 58, the 6-methyl substituted 2-pyridyl. The term unsubstituted indicates that the pyridyl ring does not have any substituents (such as a methyl or ethyl group) linked to it, while the term 6-methyl indicates that a methyl is linked to the ring at the 6 position, using the numbering system described above. Diagrams of the two compounds

are presented below:



Compound 3894



Compound 3959
Compound (b)

Compound 57 from Sohda II was designated by Takeda as Compound 3894 (“Compound 3894"), and compound 58 was designated Compound 3959 (“Compound 3959") and identified in the ‘777 Patent as compound (b). The defendants’ challenges to the ‘777 Patent largely hinge on assertions concerning these two compounds, and they will generally be referred to as compounds 3894 and (b) in the course of this Opinion.[11]

[11] As already noted, compound (b) had previously been disclosed by Takeda as compound 42 in the ‘200 Patent, and was also one of the twelve compounds later listed in the Fujita declaration that accompanied an amendment to the application for the ‘605 Patent.

The 101 compounds described by Sohda II were organized into seven groups. The article commented on characteristics associated with compounds in each of the seven groups. When discussing the group into which compounds 57 and 58 fell, it noted that "[a]lthough compounds 56, 57, 58, 59 and 63...showed potent activities, they, especially 57 and 58, caused considerable increases in body weight and brown fat weight," in the rodents in which they were tested. (Emphasis supplied.)

In the 1980's, scientists believed, as they do today, that increases in body weight are not desirable for diabetics. There was disagreement, however, about the implications of an increase in brown fat in rodents for humans treated with the same compound. Adult humans have relatively little brown (as opposed to white) fat, while rodents carry a significant amount of brown fat in the saddle between their scapulas. Brown fat has a thermogenetic effect, generating heat to keep them warm. At the time that Sohda II was written, overall weight and fat gain caused by pharmaceuticals were thought to correlate in mammals, including rodents and humans.

G. The Third Divisional Patent: The '779 Patent

On March 15, 1983, Takeda filed a third divisional patent to the '200 Patent. The application sought to expand the grouping of compounds originally covered by the '605 Patent, by adding compounds where "the pyridyl or thiazolyl groups may be

substituted."[12] A preliminary amendment also noted that compounds in which "hetrocyclic rings are substituted have become particularly important, especially Compound 42 in example 9." Compound 42 was the compound destined to be used as a comparator in the '777 Patent, where it is listed as compound (b).

Because the application only sought to expand the groups covered by the '605 Patent but not to introduce a substantively different claim, Takeda filed a terminal disclaimer, noting that the "inventive entity" covered by the '605 Patent and the application were the same, and thereby disclaiming any protection of the compounds in this application beyond the expiration of the '605 Patent. The application was approved by the PTO and issued on April 24, 1984, as U.S. Patent No. 4,444,779 ("'779 Patent").

H. The '902 Patent

Takeda's patent prosecutions were not limited to the divisionals of the '200 Patent. On December 29, 1982, Takeda filed an application covering TZD derivatives with a cyclohexane ring on the left end.[13] The patent issued on July 24, 1984 as U.S. Patent 4,461,902 ("'902 Patent").

I. The Failure of Ciglitazone

After Takeda's TZD development program attracted the interest of Upjohn, Takeda and Upjohn worked together on the

[12] A thiazolyl is a five member heterocycle, with a nitrogen and sulfur at positions 1 and 3, respectively.

[13] A cyclohexane ring is a saturated ring of six carbons. Ciglitazone's left moiety contains a cyclohexane ring.

development of ciglitazone from 1981 to 1983. Both companies analyzed the compound's anti-diabetic properties and toxicity, and based on those studies, began Phase I safety studies with human volunteers in both the U.S. and Japan.

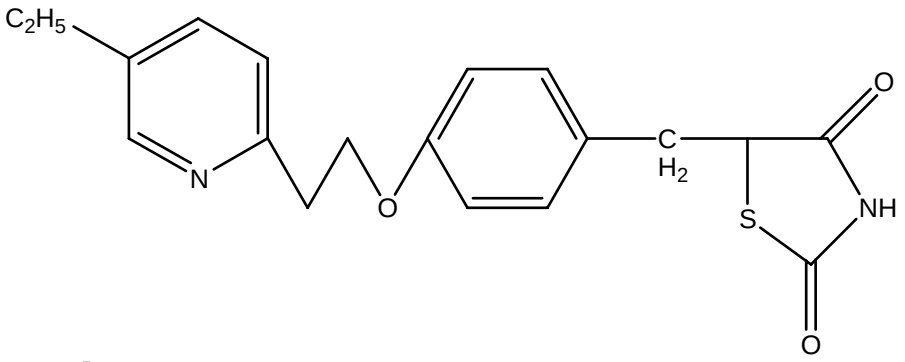
As work on the development of ciglitazone progressed it became evident that the compound could not be successful as a commercial anti-diabetic. In November 1982, it was determined that ciglitazone caused cataracts in rats that were being treated with the compound as part of a ninety-day toxicology study. Upjohn believed that the FDA would block a compound that caused cataracts from the U.S. market. Second, a clinical trial in Japan suggested that ciglitazone might not be effective for a Type 2 diabetic patient unless the dose was above 500 milligrams per day, a dosage which was impractical. By 1983, Takeda and Upjohn renewed their search for a more potent, non-toxic compound.

J. Initial Development of Pioglitazone

Meanwhile, Fujita was working with Dr. Kanji Meguro ("Meguro"), the Chief Scientist of the Chemical Research Laboratory at Takeda, to develop ideas for new compounds to be synthesized and tested. On September 7, 1982, pioglitazone was synthesized. It terminates at its left end in a 2-pyridyl ring with an ethyl at the 5 position on that ring.[14] It was given the

[14] An ethyl group is C_2H_5. Ethyl groups differs from methyl groups, CH_3, by a single CH_2 group. Ethyl and methyl are both lower alkyls.

internal Takeda compound number 4833.



Pioglitazone
Compound 4833

The first screening of pioglitazone for efficacy in November 1982 noted its promise:

> Initial Screening
> 10 Samples were tested in KKA^{y} mice. 2 samples were significant in lowering blood glucose. The effect of AD-4833 was relatively strong, 0.005% food admixture 4-day administration resulted in reducing blood glucose, plasma TG and NEFA by 46%, 31% and 30% respectively. No significant increase in body weight was observed. The effect was weaker than that of ADD-3959 [identified as compound (b) in the '777 Patent].[15]

Takeda scientists also conducted preliminary toxicity tests on compounds that showed promise. Pioglitazone was the least toxic of all the TZD compounds evaluated in 1983 and 1984.

Following the failure of ciglitazone, Upjohn and Takeda renewed their collaborative research. In their search for a new compound they focused on the 130 TZD derivatives that had been tested during the ciglitazone selection process, but also

[15]Takeda seems to have used both AD- and ADD- as prefixes when designating compounds during their research. No explanation has been given for any difference between the two prefixes. This Opinion does not use either designation.

synthesized some new compounds.

The decision by Takeda and Upjohn to continue to research TZD derivatives went against some of the thinking in the industry. Other leaders in the diabetes field believed that better avenues for research included developing insulin secretagogues (compounds which combat insulin resistance by causing the pancreas to create more insulin) and treatments for late-stage consequences of Type 2 diabetes, such as neuropathy, nephropathy, and retinpathy.

One of the compounds that was retested during this period was compound (b). Compound (b) had shown strong blood glucose lowering activity in mice and triglyceride lowering activity in both mice and rats. Despite its efficacy, compound (b) was dropped from consideration when testing revealed significant toxicity to the liver and heart as well as a decrease in the number of erythrocytes, a sign of potential toxicity to bone marrow. Compound (b) also failed the cataract screening test conducted by Upjohn.

Based on the experiences with ciglitazone and compound (b), Takeda made identifying a compound without toxic effects its highest priority. It was Upjohn's view that any compound that failed the in vitro chick lens assay test for cataractogenesis had to be ruled out from consideration for development.

K. Takeda's Testing Methods

Takeda conducted many efficacy tests on numerous compounds, including pioglitazone, throughout 1983 and 1984. In order to

screen for efficacy, KKA^{y} mice or rats were treated with different dosage levels of a compound for four days. Initial tests usually involved just two doses of the compound to determine roughly if the compound was active. The dosage levels were calculated as milligrams of compound per kilogram of body weight of the treated animal per day (mg/kg/day). The researchers typically matched the animals to be tested by age, sex and body weight. From the pools of animals, groups of five animals were randomly chosen for each dosage level in the test and a separate group of five was chosen to serve as a control. On the fifth day of the screening, the blood glucose and triglyceride levels of the test animals were measured and were compared to blood taken from untreated control animals.

For many compounds Takeda also conducted three dose efficacy tests, to assist researchers in determining the dosage of a compound necessary to reduce an animal's blood glucose level or trigylceride level by 25%. The effective dose required to reduce the levels by 25% is called the "ED^{25}".

Takeda's experiments were performed by technicians. At the end of a three dose efficacy test, the technician would perform regression calculations to plot the best straight line between the three data points. The results would then be reviewed by a trained scientist or by Fujita in order to determine whether the points plotted or the line determined by the regression equation actually corresponded as well as it should to a true dose response curve.

The relationships between two variables in biological systems, such as the changes in blood glucose concentrations with a change in a dosage of a drug, are usually not linear but rather exponential. Plotting the change of the one variable against the other will often result in a curve which is made linear through the application of a process called linear regression. There are limitations, however, on the reliability of a linear regression. A linear regression is more reliable if the interval between the data points is limited. It is significantly less reliable when the administered dosages do not fall within the effective dosage range of the compound being tested since including even one data point that is outside of the linear response region can significantly change the relationship between the three points plotted in a three-dose test. Extending a line beyond a data point to reach an ED^{25} value that was not within the tested range also runs a considerable risk that the projected results will be unreliable.

Takeda was testing new compounds whose properties were unknown and it had to guess what the best dosage range for testing might be. Not infrequently, it chose dosages that were above or below the effective dosage range. This meant that Takeda often had to conduct several experiments to improve its understanding of the effective dosage range of a compound. In addition to the challenges of making an accurate determination of the ED^{25} values, Takeda scientists also had to monitor the experiments for other possible factors that might make a

particular experiment's results unreliable.

L. Report A-15-13

On February 8, 1984, Takeda forwarded a copy of Fujita's report A-15-13 ("Report A-15-13") to Upjohn. The report, which was titled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats", disclosed the results of preliminary toxicity studies conducted on fourteen compounds that Takeda had considered as candidates for development. The report detailed the method of testing that had been employed: oral doses of 100mg/kg/day of the test compound for two weeks given to five to six week old male and female Wistar rats. At the end of the testing period the rats were sacrificed, body weights and organ weights were analyzed, as were blood chemistry and hematology. The report contained the organ weight expressed as normalized weight (calculated by dividing the organ's weight by the weight of the rat and expressing the weight as a percentage) in order to compensate for the fact that animals differ in size. Pioglitazone was one of the compounds presented in Report A-15-13 and showed no statistically significant toxicity.

In addition to pioglitazone, several other compounds of interest to this Opinion were among the fourteen, including the unsubstituted 2-pyridyl (compound 3894) and the 5-methyl 2-pyridyl (compound (c) as designated in the '777 Patent). The introduction to the report noted that each of these three compounds was less toxic "in regard to reduction of blood red

(sic) cells and hypertrophy of liver and heart which were common toxic effects in ciglitazone-related compounds." It added, "[c]onsidering the fact" that compound 3894, pioglitazone and compound (c) "are five times as potent as ciglitazone in the pharmacological activities, they appear to be much easier to continue further studies including clinical trials." In point of fact, however, the report found that compound 3894 produced a statistically significant negative effect on the heart of male rats and that compound (c) had such an impact on platelets. Two other compounds that were used as comparators in the '777 Patent also demonstrated toxicity. Compound (b) was toxic to the liver, heart and erythrocytes, among others things, while compound (d) was toxic to the liver and heart.

M. March 1984 Plan

After two days of meetings between Takeda and Upjohn in March 1984, at Upjohn's headquarters in Kalamazoo, Michigan, the participants agreed that Takeda would select fifty TZD compounds based on hypoglycemic activity in both the KKA^{y} mouse and the Wistar-fatty rat. Upjohn was to test the leads identified by Takeda in the in vitro chick lens assay for cataractogenic activity, and Takeda was responsible for other toxicity testing.[16] Takeda had already provided Upjohn with KKA^{y} mice so that Upjohn could replicate Takeda's efficacy testing. It also gave Upjohn the fifty compounds that it had synthesized and

[16] Takeda was to carrying out two-week toxicity studies for the leads in Wistar rats at 100 mg/kg/day.

selected for this intensive review.

The minutes of the March meeting reflect that it was "desirable that leads selected for further development are clean" in the chick lens assay. Based on a combination of the chick lens assay and the toxicity studies, nine to ten leads were expected to emerge and be subject to further testing by Takeda and Upjohn. It was anticipated that four to five leads would emerge from that further testing and proceed to ninety-day toxicity studies in both rats and dogs. Compounds which emerged as "clean" through all of the stages of testing would be "considered for further development with a goal of IND filing for the best compound as a drug candidate."[17] The minutes established a time line for each stage in the process. The next meeting, for selection of the nine to ten leads was scheduled for August 1984.

In selecting the fifty compounds, Takeda was also to consider the "uniqueness of chemical structure." The emphasis on the uniqueness of the chemical structure as a criterion for selecting the initial fifty compounds arose from a Takeda policy that candidate compounds should be reasonably unique from each other in their chemical structures because toxicological problems and adverse reactions are often caused by discrete chemical structures. By emphasizing variety in the chemical structures to

[17] An Investigational New Drug Application ("IND") is an application filed with the FDA to conduct clinical trials (i.e. tests on humans). Merck KGaA v. Integra Life Sciences I, Ltd., 125 S.Ct. 2372, 2377 (2005).

be studied, Takeda hoped to avoid losing entire ranges of candidates due to a particular structure's toxicity.[18] Based on those same concerns, Upjohn researchers endorsed the decision to make chemical uniqueness a selection criterion.

The fifty compounds chosen by Takeda were a mix of those that had already been tested in earlier research and those that Takeda had recently synthesized. Among the recently synthesized compounds were three that appeared as comparators in the '777 Patent: compounds (c), (d), and (e), which were first synthesized on July 21, May 4, and August 4, 1983, respectively. Because Takeda had observed that pioglitazone was comparatively potent and exhibited no toxicity it synthesized compounds that were structurally related so that it could compare the results.

Takeda's benchmark for efficacy was the ED^{25} of ciglitazone. The candidate compounds were continually evaluated from July through October of 1984 in order to find what Takeda scientists considered the most reliable ED^{25} values.

N. October 30, 1984 Meeting and Report A-15-34

Obtaining the efficacy and toxicity data for the candidate compounds turned out to be much more complicated and time consuming than expected. The meeting with Upjohn originally planned for August 1984 did not take place until the end of

[18] While Mylan argued that Takeda and Upjohn were concerned in 1984 not with identifying the best anti-diabetic treatment but with the patentability of a compound, the Takeda and Upjohn witnesses presented entirely credible testimony that they were driven by concerns about efficacy and safety. After all, a patent on a useless compound is useless.

October. At the meeting Takeda presented Fujita's report A-15-34, which was titled "Pharmacological and Toxicological Studies of Ciglitazone and its Analogues" ("Report A-15-34"). This report is of critical importance to the issues of inequitable conduct raised by defendant Mylan.

Report A-15-34 lists fifty compounds in Table 1. The report gives the chemical structure of each compound as well as efficacy and toxicity data. In generating the report, Fujita examined all of the test results to locate the most reliable ED^{25} numbers for each compound. In addition to listing the ED^{25} score which he considered to be the most reliable for each compound, Fujita also indicated in a parenthetical the relative efficacy of each compound to that of ciglitazone. For instance, the benchmark for all testing, ciglitazone, was listed first with an ED^{25} for glucose lowering in KKA^{y} mice of "40 (1)". Pioglitazone was listed about one-third of the way down the table with an ED^{25} of "6 (6.7)", indicating that a dose of 6mg (per kg per day) of pioglitazone achieved an ED^{25}, rendering it about 6.7 times more potent than ciglitazone, which required a dose of 40mg to achieve that result. The parenthetical sometimes indicated the range of the test results obtained by Takeda.

Table 1 also indicated the results of the in vitro chick lens assays conducted by Upjohn. A compound failed the chick lens assay if it caused a change in pH or a cloudy appearance at a lower concentration than did ciglitazone.

Finally, the report provided summary data for hepatomegaly

(liver toxicity), cardiomegaly (heart toxicity) and anemia (erythrocyte depletion) from two-week toxicology studies in male and female Wistar rats. The data were presented using a rating system based on the degree of toxicity. For liver and heart, toxicity was evaluated by a percentage gain in weight; for anemia, toxicity was evaluated by a percentage decrease of erythrocytes. Rather than give precise toxicity numbers, the report listed three ranges of toxicity in terms of growth or decline: 8-20%, 21-25%, and 26% and above.

Fujita selected twelve of the fifty compounds as compounds on which the meeting participants should particularly focus their attention, and presented the data for these twelve on Table 2 in the report. In selecting the twelve, Fujita considered the potency of a compound in comparison to its performance in toxicity testing, including the chick lens assay tests, as well as the structural diversity of the compounds. Fujita selected only two compounds whose left end was a pyridyl ring. One of those two was pioglitazone. Pioglitazone was the only compound among the twelve that showed no toxicity, although many of the others listed on Table 2 were far more potent. None of the comparator compounds from the ‘777 Patent appear on Table 2, although all of them appear on Table 1 of Report A-15-34.

During the meeting, the scientists from Takeda and Upjohn reviewed the data for all the compounds presented in Table 1, giving particular attention to the twelve compounds on Table 2. The discussion was an open one and Upjohn was free to suggest

that any compound from Table 1 be considered for selection as a lead.

At the meeting, Upjohn conveyed its view that low toxicity was far more important than extreme potency. Upjohn urged that the most important criterion for selection was the therapeutic ratio, that is, the difference between the effectiveness of the drug and the appearance of side effects. Due to its lack of toxicity, Upjohn pressed for the selection of pioglitazone over far more potent compounds.

In the end, Takeda and Upjohn selected five compounds from Table 2 for further testing. Pioglitazone was among the five. None of the other four ended in a pyridyl ring, and none of the others emerged as a viable candidate for commercial development from the additional testing which followed.

The decisions reached at the October meeting were vitally important to both Takeda and Upjohn. Each company intended to spend millions of dollars and valuable research resources on the selected compounds. In addition, their scientists would be spending several years of their professional lives developing the chosen compound. Having experienced a significant set back with the failure of ciglitazone, Upjohn and Takeda were looking for a compound that would validate both their focus on TZDs and their use of the KKA^{y} mouse as an effective way to test the efficacy of compounds intended to treat diabetes. Development of a safe and efficacious molecule that could be successfully developed as a pharmaceutical would validate the years Takeda and Upjohn had

invested in research.

O. Final Selection of Pioglitazone

Takeda and Upjohn continued their evaluation of the candidate compounds in late 1985 and early 1986. After more extensive toxicity studies, pioglitazone was chosen as the primary candidate for commercial development at a meeting between Upjohn and Takeda in Osaka on March 7, 1986. Pioglitazone met the important toxicity criteria: it was clean at 100 mg/kg/day in heart, liver and erythrocyte toxicity screening, as well as in the in vitro chick lens assay. Upjohn repeatedly confirmed pioglitazone's ED^{25} score.

Upjohn's decision to develop pioglitazone was not based on Takeda's data alone. Upjohn, under Colca's supervision, had conducted confirmatory efficacy and toxicity tests on over fifty of the TZD derivatives for which it received data from Takeda, including ciglitazone and pioglitazone, following experimental protocols identical to those described by Takeda in Report A-15-34. Upjohn's tests did not produce any results that were materially inconsistent with those reported to it by Takeda.

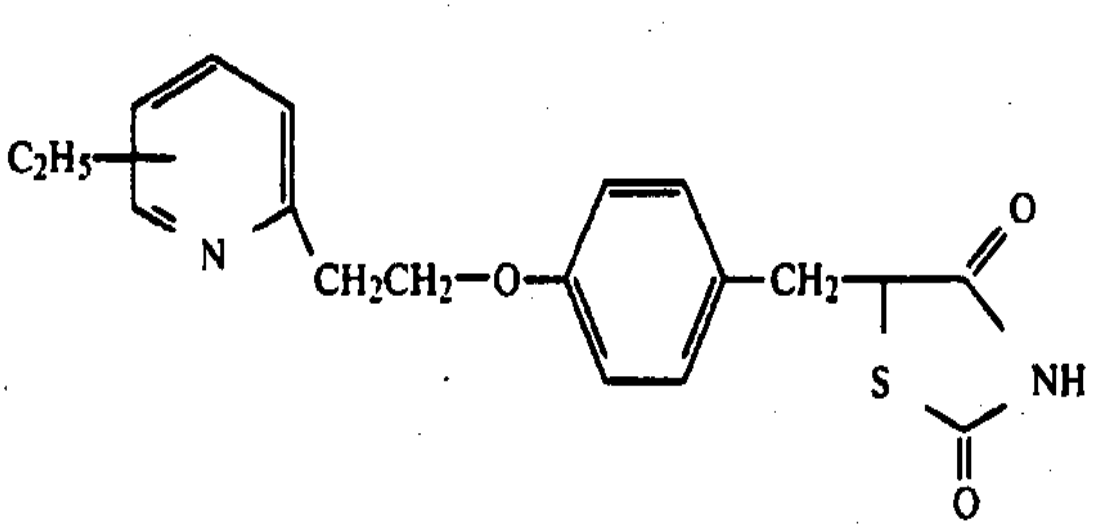
P. Prosecution History of the '777 Patent

In December 1984, Meguro submitted a request to file a patent application to Takeda's Central Research Library. The request, dated December 17, 1984, names Meguro and Fujita as joint inventors and identifies the structure of pioglitazone. The internal patent request only claims pioglitazone; there is no request to claim an ethyl substituent at any other position on

the pyridyl ring.

On January 19, 1985, Takeda filed a Japanese priority patent application covering pioglitazone, and containing the efficacy and toxicity data presented in Table 1 of the ‘777 Patent. On January 17, 1986, Takeda filed the U.S. patent application covering pioglitazone. The substance of the application was virtually identical to the Japanese priority patent application. The patent application included an Information Disclosure Statement (“IDS”) which identified relevant prior art references as including the ‘200 Patent and Sohda II.

Takeda made six claims in its application. Claim 1 was for a compound of the formula:



or a pharmacologically acceptable salt thereof.

The right end of the molecule is the defining TZD structure. For our purposes, the critical part of the formula was the left-hand portion, which was the pyridyl ring with a C_2H_5 (or ethyl group) connected to the pyridyl ring by a line leading into the middle of the ring. Drawing a line into the center of the ring means that the ethyl group can be located on any open position on the pyridyl ring.

Claims 2, 3 and 4 are dependent claims which refer back to claim 1.[19] Claim 2 is for the compound in claim 1 with the ethyl group in the 5 position, that is, pioglitazone. Claim 3 is for the sodium salt of pioglitazone. Claim 4 is for the compound in claim 1 with the ethyl group in the 6 position. This compound has never been developed by Takeda.

Takeda's application states that the purpose of its invention "is to provide compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." In support of its statement, Takeda provided efficacy and toxicity data on six compounds. The toxicity data are identical to the data presented in Report A-15-13. The efficacy data are identical to that contained in Report A-15-34.

The six compounds listed in the table are identified as (I), (a), (b), (c), (d), and (e). Compound (I) is pioglitazone. Compound (a) is ciglitazone, which has a different left end

[19] The application also included two claims that were later withdrawn.

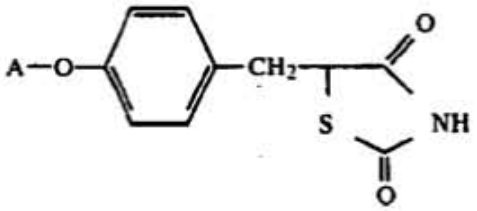
moeity than that in the other five compounds identified in the table. Ciglitazone has a methylcyclohexyl ring instead of a 2-pyridyl ring. Ciglitazone was disclosed in the prior art, having been specifically identified in both the '200 Patent and Sohda II.

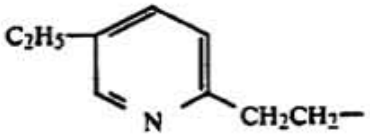
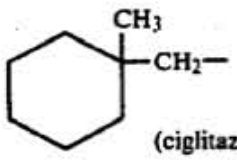
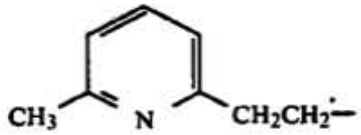
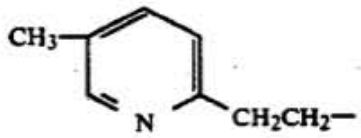
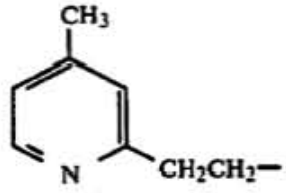
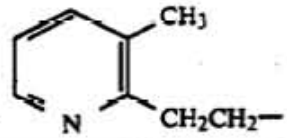
Compounds (b), (c), (d), and (e) and pioglitazone each have a 2-pyridyl ring at the left end. Compounds (b),(c), (d), and (e) have a methyl at the 6, 5, 4, and 3 positions, respectively, on the 2-pyridyl ring. Pioglitazone has an ethyl at the 5 position. Compound (b) was also specifically identified in both the '200 Patent and Sohda II.[20] Compound (c), which has the methyl in the 6 position, is the homolog of pioglitazone.[21] Table 1 of the '777 Patent is reproduced below:

[20] As has been noted previously, compound (b) was compound 42 from the '200 Patent and compound 58 from Sohda II.

[21] The term homolog describes the relationship between two compounds that differ by the addition of a repeating group, usually a single CH_2 group. An ethyl group, C_2H_5, differs from a methyl, CH_3, by a single CH_2 group.

TABLE 1



	Compound A	Blood Glucose (ED_{25})	TG(ED_{25})		Two-weeks toxicity (rat, %)					
					Liver weight		Heart weight		number of erythrocyte	
		mouse	mouse	rat	♂	♀	♂	♀	♂	♀
(I)		6	6	3	−0.7	−3.5	+0.9	−3.9	−3.4	−0.7
(a)	 (ciglitazone)	40	40	70	+6.6*	+10.8*	+13.4*	+4.0	+3.5	−0.2
(b)		4	3	5	+3.8	+10.7**	+19.9**	+17.8**	−2.9	−8.8**
(c)		20	20	—	+1.3	−1.2	+7.2	+3.0	−4.2	−6.0
(d)		20	20	—	+8.8*	+8.4**	+3.3	+7.3*	−3.7	−2.5
(e)		20	20	—	−2.3	+6.6**	+10.9	+9.8*	−8.7*	−7.0**

t-test: *P < 0.05; **P < 0.01

Comparative data on compound (b) were included in Table 1 of the patent application because it is the closest prior art. Data on ciglitazone were included, despite its clinical failures, because it was the first TZD evaluated by Takeda to show potential for use as an anti-diabetic compound and had served as an index against which to compare new compounds. The application included data on the 3, 4 and 5-methyl variants of compound (b) because the compounds were structurally close to both pioglitazone and compound (b). They were also included to emphasize that the results for pioglitazone reported in Table 1 were “quite unexpected” even when compared to its homolog, compound (c).

Two errors were made in the section which describes the method by which Takeda tested for toxicity in rats. First, the application indicates that data on toxicity were obtained using Sprague-Dawley rats, when in fact the data were obtained from Wistar rats. Both are normal strains of rats and the same methods are used to test for toxicity in either strain. The error had no implications for the validity of the test results. In previous toxicology screens, the results of studies with the two species had been comparable.

The second error involved the age of the rats used in the testing. In the patent application, the age of the rats is listed as 5 weeks old when it should have been listed as 5-6 weeks old. In the two-week toxicity tests reported in Table 1 of

the ‘777 Patent, the results for pioglitazone were obtained from rats that were six weeks old at the beginning of the two week test; the results for the other compounds were obtained from rats that were five weeks old at the beginning of the two-week experiments. The data for all the compounds were normalized to body weight to account for variation in the size of the animals, and in each test the age of rats in the control group was the same as in the group receiving the compound. The one week age difference between the five and six week old rats did not affect the validity of the comparison.

On July 1, 1986, the examiner in charge of Takeda’s U.S. patent application issued an office action (“Office Action”) requesting an explanation of how to interpret the data presented in Table 1, particularly how to “balance the need for effective ED^{25} versus the need for lower toxicity.” He rejected claims 1-5 under 35 U.S.C. § 112, quoting the section as follows:

> The specification shall contain a written description of the invention and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The Office Action also noted that Table 1 failed “to provide values for the control group.” As a result of the lack of guidance on how to read the table, the Office Action pointed out that “one of ordinary skill is not taught how to interpret the data and distinguish over the prior art.” The Office Action

requested guidance on whether there was a "therapeutic ratio" that could be used to compare the compounds and whether there was a threshold of "maximum toxicity." The Office Action concluded by asking "at what point is increased potency not desirable over increased toxicity? From the data provided one cannot conclude that [pioglitazone] is unexpectedly different from the rest."[22]

In response to the Office Action, Takeda submitted an amendment ("Amendment") and a declaration from Fujita ("Declaration"). The Amendment explained how to read Table 1, noting that the compounds (c), (d), and (e) were not disclosed in the prior art, but were tested because their chemical structure is similar to pioglitazone's. The Amendment explained how the ED_{25} values were calculated and the significance of the two-week toxicity testing in rats. It noted that only pioglitazone and compound (c) did not show any toxicity at a dose of 100 mg/kg/day for two weeks.[23] The Amendment calculated a "safety margin" for the different compounds, dividing the lowest toxic dose by the minimum effective dose. Noting that a compound with a higher safety margin is preferable, it argued that the test results showed that pioglitazone was "the most advantageous." The Amendment also explained why it was "meaningless to show the

[22] The file history for the '777 Patent reflects that three examiners, each of whom was trained in chemistry, were involved in the prosecution. Their annotations to Sohda II and Table 1 show particular attention to prior art compound (b).

[23] As previously noted, pioglitazone and compound (c) are the only compounds in Table 1 with substituents at position 5 on the 2-pyridyl ring.

values of the control" if one is skilled in the art.

In order to complete the safety margin calculations, Fujita's Declaration added calculations for rat triglyceride ED^{25} values for three compounds. These values were the only omissions in the columns of data presented in Table 1. Fujita asked his researchers to perform the experiments to generate the missing triglyceride ED^{25} data for compounds (c), (d), and (e). The report from the researchers who conducted the experiments showed ED^{25} data for two of the compounds but reported that compound (d) showed no effect. Fujita chose to take the ED^{25} rat triglyceride data for the third compound from Report A-15-34.

The experiments for rat triglyceride values for compounds (c) and (e) were performed by an experienced technician and supervised by an experienced researcher. During the experiment, the supervisor decided to exclude a control rat from consideration. It was common at Takeda to give researchers discretion not to use data from a single outlier animal.

Takeda filed its Amendment and the accompanying Declaration from Fujita with the PTO in November 1986. The PTO issued a Notice of Allowability on January 6, 1987. The patent issued on August 18, 1987. The '777 Patent was originally set to expire on January 17, 2006. The patent term was extended by five years to January 17, 2011, pursuant to a petition filed by Takeda under the Hatch-Waxman Act.

Q. Upjohn Abandons Pioglitazone

Upjohn ended its collaboration with Takeda in September of

1993. In doing so, Upjohn considered an upcoming "milestone" payment due to Takeda, its desire to leave the diabetes market, and its concern about litigation risks associated with launching a new drug. Upjohn management also had concerns about some of the results from longer term toxicity studies on pioglitazone. The Upjohn scientists most directly involved in supervising the development of pioglitazone disagreed with the decision and were deeply disappointed by it. Upjohn's decision contributed to the long delay between the '777 Patent issuing and the FDA approving ACTOS®, a delay which resulted in pioglitazone being the third TZD, instead of the first, to reach the U.S. market.

R. Combination Uses

Takeda has received seven patents for pioglitazone to be used in combination with other drugs ("Combination Use Patents"). All but one of the Combination Use Patents expire on June 16, 2016; one expires on August 9, 2016. As already noted, it is common for diabetics to be treated with several drugs at the same time, each targeting a different body mechanism associated with the disease.

S. Marketing ACTOS®

The FDA approved ACTOS® in July 1999. Before May 1998, Takeda had no wholly owned United States sales entity. Takeda North America was created in May 1998 to market ACTOS® in the United States. In preparation for the launch of ACTOS®, Takeda Pharmaceuticals America, Inc. ("TPA"), the predecessor to Takeda North America, entered into a license agreement with Takeda which would allow Takeda North America to sell and market ACTOS® in the

United States. TPA also entered into an agreement on December 14, 1998 with Eli Lilly and Company, which required Eli Lilly to co-promote ACTOS® with Takeda North America.

T. Hatch-Waxman Act[24]

The introduction of new drugs in the U.S. market is governed by the Federal Food, Drug and Cosmetic Act, which prohibits the introduction into interstate commerce of "any new drug, unless an approval of an application filed pursuant to subsection (b)" of 21 U.S.C. § 355 "is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) describes the process of filing a New Drug Application ("NDA") with the FDA. The process of filing an NDA is typically costly and time-consuming. In the case of pioglitazone, for example, it took almost 12 years from the issuance of the '777 Patent until pioglitazone (in the form of pioglitazone hydrochloride) was approved by the FDA for the treatment of Type 2 diabetes on July 15, 1999.

In 1984, in order to accelerate the approval process for low-cost generic versions of established drugs, Congress enacted the Hatch-Waxman Act. Among other things, the Hatch-Waxman Act added subsection (j) to Section 355. Hatch-Waxman Act § 101. Subsection (j) provides for the filing of an Abbreviated New Drug Application ("ANDA") with the FDA for the bioequivalent form of a drug already approved for safety and effectiveness. 21 U.S.C. § 355(j)(1), (j)(2)(A), (j)(7)(A). Subsection (j)(7)(A) further

[24] This treatment of the Hatch Waxman Act draws significantly from the description in In re Tamoxifen Citrate Antitrust Litig., 429 F.3d 370, 374-77 (2d Cir. 2005).

provides that the Secretary of the FDA will create and maintain a list of such approved drugs. Id. §355(j)(7)(A). This list, Approved Drug Products with Therapeutic Equivalent Evaluations, is commonly known as the "Orange Book." See id.; http://www.fda.gov/cder/ob/default.htm.

When filing an ANDA, the filer must also include, with the application, "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug...." 21 U.S.C. § 355(b)(1). An ANDA filer must certify, with respect to each patent that claims the listed drug, either that no patent was filed for the listed drug (a "paragraph I" certification), that the patent has expired (a "paragraph II" certification), that the patent will expire on a specified date and the ANDA filer will not market the drug until that date (a "paragraph III" certification), or that the patent is invalid or would not be infringed by the manufacture, use, or sale of the new drug (a "paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii).

An ANDA filer that elects a paragraph IV certification must notify each affected patent owner of the certification. Id. § 355(j)(2)(B)(I). The patent owner then has forty-five days after the date it receives such notice to bring suit against the ANDA filer for patent infringement. Id. § 355(j)(5)(B)(iii). If no patent owner brings such a lawsuit during this period, the FDA may immediately approve the ANDA. Id. If, however, the patent owner brings suit during this period, the FDA's final approval of the ANDA is stayed for thirty months after the date the patent

owner received the requisite notice,[25] or until a district court returns a decision as to the validity of the patent or its infringement if it does so before the thirty-month period expires. Id.

ANDA applicants may also satisfy their obligation to address all relevant patents by filing a statement under 21 U.S.C. 355(j)(2)(viii) ("Section viii Statement"). By filing a Section viii Statement the applicant acknowledges that the drug sought to be manufactured is protected by a method of use patent, but claims that the applicant is not seeking approval for the patented use. An ANDA filer can submit either a Section viii Statement or a paragraph IV certification for each listed patent, but not both. See Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 880 (D.C. Cir. 2004).

Any approval letter sent by the FDA before the expiration of the prescribed stay and before a court ruling of patent invalidity or non-infringement is tentative. See 21 C.F.R. § 314.105(d). If before the thirty months expire a court rules that the patent is either invalid or not infringed, the tentative approval of the ANDA is made effective as of the date of judgment. 21 U.S.C. § 355(j)(5)(B)(iii)(I). If after thirty months there has been no ruling on patent validity or infringement and the stay expires, the ANDA filer can distribute and market the drug but, depending on the court's later patent

[25] The notices of paragraph IV certification that Takeda received from Mylan and Alphapharm are dated September 8, 2003, and January 29, 2004, respectively. Thus, the 30 month periods will run on March 8 and July 29, 2006.

ruling, an ANDA filer that chooses to follow this course may thereafter become liable for damages if infringement is found. In re Tamoxifen, 429 F.3d at 376.

As an incentive for generic manufacturers to choose the paragraph IV certification route, and thereby to challenge weak patents, the Hatch-Waxman Act offers under certain conditions, the first ANDA filer with a paragraph IV certification the opportunity to market its generic drug exclusively for 180 days. To this end, the FDA may not approve the ANDA of a subsequent filer until 180 days after the earlier of the date 1) the first ANDA filer commercially markets the generic drug, or 2) a court of competent jurisdiction concludes that the patent in question is invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II).[26]

Alphapharm was the first to file an ANDA. Its submission to the FDA was ultimately rejected because it could not make a pill that was a bioequivalent to ACTOS®.[27] As a result, the second filer, Mylan, will enjoy the six month exclusivity period if the

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[26] Until 1998, the 180 day exclusivity period was available to the first ANDA filer to elect a paragraph IV certification only if it successfully defended a lawsuit for infringement of the relevant patent. See 21 C.F.R. § 314.107(c)(1)(1995). This "successful defense" rule was challenged and rejected by circuit courts in two separate lawsuits. See, e.g., Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1076 (D.C. Cir. 1998). The FDA formally revoked the "successful defense" requirement in 1998. See Effective Date of Approval of an Abbreviated New Drug Application, 63 Fed. Reg. 59,710, 59,710 (Nov. 5, 1998), 21 C.F.R. § 314.107 (1999).

[27] It appears that the FDA rejected Alphapharm's ANDA at some point between its initial filing in July 2003, and its filing of a Section 355 Statement in January 2004.

‘777 Patent is invalidated.

U. The Defendants’ ANDA Filings

On July 15, 2003, Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Danbury Pharmacal, Inc. (“Watson”), Alphapharm, Ranbaxy Laboratories, Ltd., and Ranbaxy Pharmaceuticals, Inc. (“Ranbaxy”), and Mylan all filed ANDAs seeking approval to market 15 mg, 30 mg, and 45 mg pioglitazone hydrochloride tablets. Ranbaxy and Watson filed paragraph III certifications with respect to the ‘777 Patent; they did not challenge its validity, representing instead that they will not make, use, sell, or offer for sale their products until the expiration of the ‘777 Patent. Both Ranbaxy and Watson also filed paragraph IV certifications relating to the composition claims in the Combination Use Patents.[28]

Alphapharm filed a paragraph IV certification claiming that the ‘777 Patent is invalid. Alphapharm filed a Section viii Statement with the FDA with respect to the Combination Use Patents, asserting that it does not seek approval for any of the uses covered by those patents.

Mylan filed a paragraph IV certification with respect to the ‘777 Patent, claiming that it is invalid. With respect to the Combination Use Patents, Mylan filed a paragraph IV certification addressing the pharmaceutical composition claims of one of the patents and a Section viii Statement regarding the method claims.

[28] Ranbaxy also included, with its Paragraph IV certification, Section viii Statements with respect to the method claims contained in the Combination Use Patents.

V. The Alphapharm and Mylan Statements of Obviousness

In their paragraph IV certifications, both Alphapharm and Mylan claimed that the '777 Patent was invalid due to obviousness. Alphapharm and Mylan were required to send a notice of paragraph IV certification that included detailed statements of the legal basis of their positions that the '777 Patent was invalid ("Section 355 Statement"). See 21 U.S.C. § 355(j)(2)(b)(ii). By the time of trial, each defendant had radically altered the approach to the invalidity issue expressed in its statement. Mylan abandoned its articulated theory of obviousness in its entirety, and pursued an inequitable conduct claim at trial. Alphapharm altered its obviousness argument in several substantial ways. The following describes the parties' Section 355 Statements and compares them to the positions they took at trial.

Alphapharm's Section 355 Statement, dated January 29, 2004, recognized that it had the burden to prove by clear and convincing evidence that the prior art must provide some reason or motivation for a person of ordinary skill to make pioglitazone. It identified only two sources of prior art: the '200 Patent and Sohda II. As its position at trial evolved, it also argued that the divisional patents to the '200 Patent and a few articles in scientific journals were also prior art.

Insofar as the '200 Patent was concerned, Alphapharm argued in the Statement that the patent generically disclosed pioglitazone, and identified three compounds related to

pioglitazone: compounds 16, 40, 42.[29] It noted that compound 42 is the methyl homolog of the ethyl compounds covered by Claim 1 of the '777 Patent, and argued that an exchange of an ethyl group for a methyl group would have been obvious.

Next, relying on the fact that two compounds discussed in Sohda II, compounds 11 and 14, are revealed in that article to have identical efficacy and yet differ only in that one has an ethyl substituent and another has a methyl substituent, Alphapharm contended that one of ordinary skill would conclude that the methyl and ethyl are "equivalent with respect to biological activity on a closely related analog of pioglitazone." In making this assertion, Alphapharm identified each compound as attached to a pyridyl ring. Neither compound has a pyridyl ring as its left end moeity and Alphapharm does not argue at trial that they do.[30]

At trial, Alphapharm concentrated on an entirely different compound described in Sohda II. It argued that the discussion in Sohda II of compound 58 (which had a higher combined efficacy score than either compound 11 or 14) would have led one of ordinary skill in the art to choose compound 58 as the lead compound for further development. That argument is not to be found in Alphapharm's Section 355 Statement.

Alphapharm also argued in its Section 355 Statement that

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[29] Compound 16 has an ethyl substituent on a phenyl ring. Compound 40 is the unsubstituted pyridyl ring known as compound 3894. Compound 42 has a 6-methyl substituent on a pyridyl ring; it is compound (b).

[30] A benzene ring is at the left end of each compound.

both the ‘200 Patent and Sohda II identify ciglitazone as having low toxicity, and that Takeda did not demonstrate that pioglitazone was surprisingly superior to ciglitazone. Similarly, it contended that the ‘777 Patent alleges an entirely different activity for ciglitazone than was disclosed in Sohda II. Alphapharm did not pursue either theory concerning ciglitazone at trial.

Next, Alphapharm’s Section 355 Statement argued that Table 1 in the ‘777 Patent does not support the superiority of pioglitazone, and that the testing methodology described in the patent is flawed. Specifically, Alphapharm argued that “many” of the toxicity values on Table 1 were not “statistically significant.” Alphapharm did not make this argument at trial.

Alphapharm argued in its Section 355 Statement that the experiments underlying the testing of a compound’s toxicity to the heart were “inherently flawed” since Table 1 in the ‘777 Patent indicated that pioglitazone did not cause heart enlargement with a dose of 100 mg/kg, while the prescribing information for ACTOS® advises that heart enlargement was observed at 4 mg/kg in rats. The screening tests that produced the Table 1 data were, as described in the Patent’s Application, two-week tests. The tests to which the ACTOS® disclosure refers were long-term tests conducted by Upjohn in 1992. Alphapharm tried to use this flawed post-hoc reasoning at trial, and that effort was rejected.

In its Section 355 Statement, Alphapharm next argued that the examiner should not have found that Takeda presented

sufficiently compelling evidence to overcome the prima facie obviousness of pioglitazone. It pointed to the efficacy data for the rats, which showed that the ED^{25} values for all of the pyridyl ring compounds were comparable and that all have strong pharmacological activity. In a related argument, Alphapharm contended in its Section 355 Statement that Takeda did not present any data to the examiner to establish that the other three ethyl 2-pyridyl compounds covered by Claim 1 had surprising or unexpected results. At trial, the thrust of Alphapharm's evidence concerned compound (b), which Table 1 revealed was potent in both mice and rats, but highly toxic. Alphapharm did, however, particularly in its summation, try to fashion an argument about the ethyl compounds other than pioglitazone that are covered by the patent.

Mylan's Section 355 Statement, dated September 8, 2003, was far more straightforward. It also identified only two relevant pieces of prior art, the '200 Patent and Sohda II. It argued simply that one compound described in both, which had a benzene ring at the left end instead of a pyridyl ring, and which was identified in Sohda II as having high efficacy,[31] made the invention of pioglitazone obvious. According to Mylan, the two compounds are "bioisosteres," and their structural similarity made it obvious to replace a benzene ring with a pyridine ring.

Mylan incorrectly described the benzene compound both in terms of its structural relationship to pioglitazone and in terms

[31] The benzene compound is compound 16 in the '200 Patent and compound 14 in Sohda II.

of its efficacy.[32] In any event, Mylan completely abandoned this theory of obviousness during the discovery period. It proceeded to trial on an inequitable conduct claim.

W. Procedural History

On September 16, 2003, Takeda sued Mylan, Watson and Ranbaxy. Takeda sued Alphapharm on March 12, 2004. Takeda alleged direct infringement of the claims of the '777 Patent against Mylan and Alphapharm, and sought a declaratory judgment of induced infringement of the claims of the Combination Use Patents against all four defendants. Takeda's action against Alphapharm was accepted as a related to the other three actions on March 18, 2004. In their answers, Mylan and Alphapharm both asserted that the '777 Patent was invalid on the ground of obviousness. Defendant Watson moved to dismiss as non-justiciable those claims in Takeda's complaint that alleged induced infringement of the Combination Use Patents. Watson's motion was denied because Takeda alleged "a controversy of sufficient immediacy." Takeda Chem. Indus., Ltd. v. Watson Pharm., Inc., 329 F. Supp. 2d 394, 403 (S.D.N.Y. 2004). A July 20, 2004 Order set May 27, 2005 as the date by which fact discovery would end, and set January 16, 2006 as the trial date.[33]

Alphapharm moved to dismiss nine of Takeda's claims relating

[32] The compound had a combined efficacy score of 5; many compounds had higher scores.

[33] The trial date was later moved to January 17, 2006, due to a federal holiday.

to the Combination Use Patents on May 21, 2004. On the same day, Takeda moved to dismiss Alphapharm's affirmative defense and counterclaim for "patent misuse." Alphapharm's motion was denied by Order dated August 13, 2004. Takeda's motion to dismiss was granted in an Opinion that noted that Alphapharm had failed "to meet even the minimal requirements of notice pleading." Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., 04 Civ. 1966 (DLC), 2004 WL 1872707 (S.D.N.Y. Aug. 19, 2004).

Mylan's substitution of an inequitable conduct claim for its obviousness theory occurred in 2005. By letter dated March 15, 2005, Mylan noted that it could not locate experiments in Takeda's laboratory notebooks to support all the data submitted to the PTO and raised for the first time an argument that Takeda may have procured the '777 Patent "through inequitable conduct." On April 25, in response to a contention interrogatory from Takeda, Mylan formally contended for the first time that the '777 Patent was unenforceable on the basis that Takeda had committed inequitable conduct in its prosecution of the '777 Patent.[34] On June 6, after the close of fact discovery, Mylan served supplemental responses to Takeda's interrogatories, in which it expressed the view that the '777 Patent was invalid on the basis of obviousness over compound 57 from Sohda II,[35] a different

[34] Despite this notice, in early June, Mylan's counsel refused to let the company's Rule 30(b)(6) witness explain the bases for Mylan's contention that the '777 Patent is invalid on grounds other than those disclosed in the Mylan's Section 355 Statement.

[35] Compound 57 is Takeda compound 3894, the unsubstituted 2-pyridyl.

compound from the one identified in Mylan's Section 355 Statement. Mylan's effort to substitute a new theory of obviousness was rejected in an Order of June 15. Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253 (DLC), 2005 WL 1457696, at *2 (S.D.N.Y. June 15, 2005). See also Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253 (DLC), 2005 WL 2092920, at *1 (S.D.N.Y. Aug. 31, 2005). Meanwhile, on June 15, Mylan was given leave to amend its answer to add a claim for inequitable conduct, essentially because of the "desire that issues, if at all possible, be addressed on the merits in litigation." Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253 (DLC), 2006 WL 44053, at *1 n.2 (S.D.N.Y. Jan. 9, 2006). Given its late notice of this new claim, Mylan was required to present all bases for the claim in its expert reports.

All four actions were consolidated for trial by Order dated October 13, 2005, although the '777 Patent issues were to be tried before the issues relating to the Combination Use Patents. By Order of December 30, 2005, the trial on the Combination Use Patents was severed.

Takeda, Alphapharm and Mylan moved in limine to strike testimony by or to preclude certain witnesses. Takeda moved against Mylan experts Hendry, Nusbaum, and Ronis. Alphapharm moved against Takeda experts Hendrickson, Inzucchi, Kettyle, Koller and Stoner. Mylan moved against Stoner and to exclude a supplemental declaration from Landau. Mylan also moved to preclude Takeda from offering evidence of any missing laboratory

notebooks.

Ronis' testimony was stricken to the extent it was not contained in his expert report. Id. at *2. Hendry's testimony was stricken to the extent it covered areas in which he had denied having expertise. Id. at *2-3. The motions addressed to testimony by Nusbaum and Stoner were granted to the extent they offered legal argument or opinions that went beyond their expertise. Id. at *3; Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253 (DLC), 2006 WL 137374, at *2 (S.D.N.Y. Jan. 9, 2006). Landau's supplemental declaration was stricken. Takeda, 2006 WL 444053, at *3. Mylan's motion to exclude evidence of any missing notebooks was denied. Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253 (DLC), 2006 WL 83112 (S.D.N.Y. Jan. 12, 2006).

Hendrickson's testimony was stricken to the extent he opined on the selection of lead compound. Takeda, 2006 WL 137374. The motions concerning Koller, id. at *2, and Inzucchi and Kettyle were denied, Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 03 Civ. 8253, 2006 WL 66480 (S.D.N.Y. Jan. 12, 2006).

At trial Mylan offered into evidence the unredacted declarations from Hendry and Ronis that it had served with the Joint Pretrial Order. The unredacted Ronis declaration was submitted as an Offer of Proof pursuant to Rule 103 of the Federal Rules of Evidence. In making its Offer of Proof, Mylan emphasized that it was not seeking to make a motion for reconsideration of the Court's decision to strike parts of Ronis' testimony, Takeda, 2006 WL 44053, and it is not being treated as

such.[36]

Discussion

Alphapharm asserts that pioglitazone is obvious in light of the prior art. Mylan contends that Takeda engaged in inequitable conduct. For the following reasons, each of these arguments is rejected.

I. Obviousness

Inherent in the Constitution's grant of patent power to Congress is the requirement that a patent monopoly be conveyed only where there is "[i]nnovation, advancement, and things which add to the sum of useful knowledge." Graham v. John Deere Co., 383 U.S. 1, 6 (1966). Through the 1952 Patent Act, Congress codified three conditions for patentability: novelty, utility, and non-obviousness. Id. at 17; 35 U.S.C. § 101-103. It is the last of these three conditions on which Alphapharm rests its challenge to Takeda's '777 Patent.

A patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §

[36] At trial, Takeda presented its evidence first. At the close of Takeda's case on January 25, both Takeda and Alphapharm moved for judgment as a matter of law under Rule 52(c). Fed. R. Civ. P. 52(c). Alphapharm had not carried its burden of showing obviousness at that point, and did not do so either through its later presentation of its own evidence. Since the burden rested on Alphapharm, it was not appropriate to grant Takeda's motion until Alphapharm had had an opportunity to present its case.

103(a) (emphasis supplied). Section 103 emanates from the Supreme Court's nineteenth century decision in Hotchkiss v. Greenwood, 52 U.S. 248 (1850), and its progeny, which took a functional approach to patent analysis and eschewed labels. Graham, 383 U.S. at 12, 17. The talismanic statement of the obviousness inquiry appears in Graham, which identifies four factual underpinnings to a determination of obviousness: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claimed invention, and (4) objective indicia of non-obviousness. Id. at 17-18; see Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1372-73 (Fed. Cir. 2005). The issue of obviousness is a question of law. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997).

The scope and content of the prior art includes art that is "reasonably pertinent to the particular problem with which the invention was involved." Ruiz v. A.B. Chance Co., 234 F.3d 654, 664 (Fed. Cir. 2000) (citation omitted). Prior art must be available before the date of invention. 35 U.S.C. § 103(a), see Richardson-Vicks Inc., 122 F.3d at 1480. Prior art teaches away from an invention "when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention." Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371, 1380 (Fed. Cir. 2005).

Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. Ruiz, 234 F.3d at 666. In determining what

constitutes ordinary skill in the art, a court may consider "1) the types of problems encountered in the art; 2) the prior art solutions to those problems; 3) the rapidity with which innovations are made; 4) the sophistication of the technology; and 5) the educational level of active workers in the field." Id. at 666-67.

Secondary considerations or the objective indicia of non-obviousness include "commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." Id. at 662-63. These considerations are probative to the extent they "give light to the circumstances surrounding the origin of the subject matter sought to be patented." Graham, 383 U.S. at 17-18. The "nexus" or causal relationship between the secondary consideration and the claimed invention should shed light on whether the invention was obvious or not. See Merck, 395 F.3d at 1376. A presumption that a patented invention is commercially successful arises when a patentee can demonstrate "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1377 (Fed. Cir. 2000) (citation omitted).

Patents are presumed to be valid. 35 U.S.C. § 282. A party challenging a patent can establish a prima facie case of invalidity by showing that the invention is obvious under an analysis of the first three Graham factors. Winner Intern. Royalty Corp. v. Wang, 202 F.3d 1340, 1350 (Fed. Cir. 2000). If a prima facie case of obviousness is established, the burden of

production shifts to the party defending the patent to demonstrate non-obviousness under the fourth Graham factor. Id. The burden of persuasion, by clear and convincing evidence, always remains with the party asserting the invalidity of the patent. Beckson Marine, Inc. v. NFM, Inc., 292 F.3d 718, 725 (Fed. Cir. 2002). The burden is "especially difficult" if the challenger relies on prior art "that was before the patent examiner during prosecution." Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1348 (Fed. Cir. 2004) (citation omitted). This added burden stems from the "deference that is due to a qualified government agency presumed to have properly done its job." Ultra-Tex Surfaces, Inc. v. Hill Brothers Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000) (citation omitted).

A strand of the law of obviousness addresses patents protecting chemical compounds. In the case of a chemical compound, a prima facie case of obviousness exists where there is a "structural similarity between claimed and prior art subject matter" and "the prior art gives reason or motivation to make the claimed compositions." Yamanouchi Pharm. Co., Ltd. v. Danbury Phamacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000)(citation omitted). "[O]bviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention." Beckson, 292 F.3d at 727. Thus, an invention is prima facie obvious where the prior art would imbue one of ordinary skill in the art with a "reasonable expectation of success" in achieving the goals that the inventor sought to accomplish by transforming

a compound in the prior art into the structurally similar claimed invention. Yamanouchi, 231 F.3d at 1343 (citation omitted). While a reasonable expectation of success must be shown, in order to show prima facie obviousness it is not necessary to show that success was absolutely predictable. Id.

Where the creation of a chemical compound requires the chemist to pursue several steps in manipulating a compound revealed in the prior art, the patent challenger must show that one of ordinary skill in the art would have had sufficient motivation to take each of those steps. Id. at 1344-45. Similarly, if the prior art "offers no suggestion to pursue the particular order" of manipulations that led to an invention, and where a deviation in the order would have taught away from the invention, then the challenger must show what would have led any ordinary artisan in the field "to follow the precise steps that produced a remarkable invention." Id. at 1345.

A prima facie case of obviousness may be rebutted by "showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." Dillon, 919 F.2d at 692-93. When rebuttal evidence is submitted, "all the evidence must be considered anew." In re Eli Lilly and Co., 902 F.2d 943, 945 (Fed. Cir. 1990); see also Glaxo Group Ltd., 376 F.3d at 1349; Richardson-Vicks, 122 F.3d at 1482-83.

Alphapharm contends that pioglitazone is prima facie obvious over the prior art compound (b) from Table 1 of the '777 Patent, which had been identified in both the '200 Patent and Sohda II.

Alphapharm argues that the prior art clearly identified compound (b) as a lead compound warranting further investigation, and that the application of a few, obvious chemical processes would have produced pioglitazone. Turning to objective evidence of pioglitazone's obviousness, Alphapharm contends that pioglitazone's lack of toxicity is not unexpected because variability among compounds is "inherent". As for its commercial success, Alphapharm argues that the success of ACTOS® must be discounted because inter alia pioglitazone was not the first TZD on the market and is not the only successful TZD still on the market. These and Alphapharm's other arguments are described in detail below.[37]

Alphapharm's arguments fall woefully short of the mark. The prior art did not disclose or suggest either the pioglitazone molecule itself or how to make it. Alphapharm has not shown by any persuasive evidence, much less by clear and convincing evidence, that one with ordinary skill in the art would have had any reasonable expectation based on the prior art that synthesizing pioglitazone would result in the discovery of a non-toxic, effective treatment for diabetes, and therefore would not have had any motivation to do so. To begin with, the evidence is overwhelming that one skilled in the art would not have, based on the prior art, chosen compound (b) as a lead compound. Beyond

[37]It has been challenging to capture Alphapharm's arguments because it has presented a constantly shifting set of arguments, abandoning some, inventing others, and even contradicting itself as the trial progressed. Nonetheless, every effort has been made to address each of the principal arguments raised during the trial by Alphapharm.

that, Alphapharm has not shown that the ordinary artisan would have had sufficient motivation to take each of the several conceptual and experimental steps that were necessary to move beyond compound (b) and create the pioglitazone molecule.

Even if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected. Alphapharm is unable to overcome the extreme differences in the toxicity profiles between pioglitazone and prior art compound (b), whose modification it contends would have led to the discovery of pioglitazone. Confronted with overwhelming evidence that the non-toxicity of pioglitazone was entirely unexpected given the high toxicity of compound (b), including the admission of Alphapharm's own expert that there was no reasonable basis to expect that pioglitazone would be non-toxic, Alphapharm ignores the relevant legal standard and argues simply that there is so much variability in the pharmacological effects of compounds, even compounds that share similar structures, that a compound's non-toxicity is "not surprising." This does not carry Alphapharm's burden of showing obviousness. The discussion that follows examines each of the Graham factors, paying particular attention to the identification of a lead compound, the motivation to alter that compound, and unexpected results.

A. Qualifications of a Person of Ordinary Skill in the Art

The parties agree that a person with ordinary skill in the art would have a graduate degree in chemistry or a relevant branch of chemistry and practical experience applying that

education by working at or consulting with a pharmaceutical company in the development of pharmaceutical compounds.[38] It is unnecessary to refine further the minimum qualifications of a person with ordinary skill in the art, since nothing that follows in this analysis turns on the presence of a more precisely drawn definition.

Alphapharm has argued that one of Takeda's experts, Danishefsky, is not qualified to opine about what one with ordinary skill in the art of medicinal chemistry would understand or do since he is a synthetic organic chemist. Danishefsky is a renowned synthetic organic chemist who has devoted his entire career to exploring the issues of medicinal chemistry.[39] He supervises the training of medicinal chemists, has recently been nominated to receive a lifetime achievement award in chemistry from a major pharmaceutical company,[40] and regularly consults

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[38]Alphapharm defines someone of ordinary skill in the art as a person who would have secured a Ph.D. in medicinal chemistry or a related field, done postdoctoral work for two to three years and thereafter worked for a pharmaceutical company for two to three years. Takeda defines the person as someone with a Master's Degree in chemistry or chemical engineering with four years experience in the research and development of pharmaceuticals or medical organic compounds, or someone with a Ph.D. in chemistry or chemical engineering with two years of experience in the research and development of pharmaceuticals or medicinal organic compounds.

[39]Takeda brought to this trial experts of extraordinary accomplishment and distinction. Many of them, including Danishefsky, were preeminent in their field of endeavor. These were scientists whose knowledge and opinions were uniformly helpful to the Court in understanding the science at issue here.

[40] Danishefsky will receive a lifetime achievement award from Bristol-Myers Squibb in May 2006 and the National Academy of Science's medal in chemical sciences in April 2006.

with major hospitals and pharmaceutical companies on issues of medicinal chemistry. He is superbly qualified to opine in the field of medicinal chemistry.

B. Relevant Prior Art

As noted above, Takeda applied in Japan for what became known as the '777 Patent in January 1985, and in the United States in January 1986; the '777 Patent issued on August 18, 1987. It is undisputed that the relevant prior art for the '777 Patent includes the '200 Patent, issued in 1981; and Sohda II, published in 1982, both of which were identified by Takeda in its application for the '777 Patent. The '200 Patent first disclosed the compound on which Alphapharm relies for its obviousness argument, compound (b).[41] Alphapharm's expert identifies Sohda II as the "key" piece of prior art on which the skilled artisan would have relied to identify compound (b) as the lead compound for further investigation.[42]

Although Alphapharm's Rule 30(b)(6) witness testified that Alphapharm was not aware of any prior art that Takeda failed to put before the examiner, at trial Alphapharm identified two additional patents and one other article as prior art. It asserts that two divisional patents for the '200 Patent, the '605 and '779 Patents, issued on July 20, 1982, and April 24, 1984,

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[41]Compound (b) from Table 1 is a 6-methyl, which was identified in the '200 Patent as compound 42.

[42] While Alphapharm began the trial by identifying Sohda II as the critical writing which would have led one skilled in the art to identify compound (b) as a lead compound, in the face of overwhelming evidence to the contrary, by the end of the trial it had virtually abandoned reliance on Sohda II.

respectively, and their prosecution histories, should also be considered relevant prior art.[43] In particular, it asserts that the prosecution history of the '779 Patent, which was available to the public through examination in Washington, D.C. when the '779 patent was issued, would have assisted those with ordinary skill in the art in selecting compound (b) as a lead compound for further investigation. Finally, Alphapharm identifies an article in a peer reviewed scientific journal: Nohara, A. et al., "Studies of Antianaphylactic Agents. 6.1 Synthesis of Some Metabolites of 6-Ethyl-3(1H-tetrazol-5-yl)chromone and their Analogues," Journal of Medicinal Chemistry, 22:3, 290-295 (1979)("Nohara Article").[44] Mosberg gleaned from the Nohara Article that persons of ordinary skill in the art, including Takeda, practiced the synthesis of routine homologs to improve promising drug compounds as of 1979.

C. Differences Between the Prior Art and Pioglitazone

Alphapharm's assertion of obviousness rests on two claims: that it would have been obvious to select a single compound from the prior art –- a 6-methyl on a pyridyl ring, which is compound (b) on Table 1 of the '777 Patent -- as the "lead compound" for

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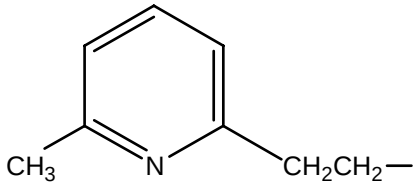
[43] Takeda disputes that these patents can properly be considered prior art.

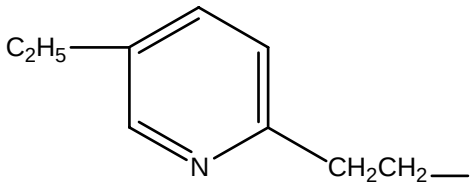
[44] Alphapharm has abandoned its contention that a second article, Cunningham, S. et al., "The Characterization and Energetic Potential of Brown Adipose Tissue on Man", Clinical Science 69, 343-348 (1985)("Cunningham Article"), was prior art. Alphapharm's expert used the Cunningham Article to educate himself about how persons of ordinary skill viewed the issue of brown fat in the 1980's. Compound (b) was identified in Sohda II as increasing brown fat.

development, and that it would have been obvious to create and test the compounds that lie between the 6-methyl and pioglitazone, which is a 5-ethyl on a pyridyl ring.[45] The program would have entailed synthesizing compounds in which a methyl appears at each of the open positions on the pyridyl ring, a process that Alphapharm terms “walking the ring”, and also synthesizing compounds in which the substituent on the pyridyl ring at each of these positions is an ethyl instead of a methyl, a process referred to as “homologation”.

The following diagrams of the left end of compound (b) and pioglitazone illustrate the changes in the molecular structure that were necessary to make the transformation.



Compound (b)



Pioglitazone

[45] As already noted, a methyl group contains one carbon, while an ethyl group contains two carbons.

Both of these structures are on a pyridyl ring.[46] Compound (b) has a substituent added at the 6th position on the ring; pioglitazone's substituent is added at the 5th position, counting counter-clockwise from the nitrogen atom on the ring.

1) Identification of a Lead Compound

Alphapharm's obviousness argument relies in the first instance on its contention that one skilled in the art would have recognized compound (b) as the lead compound for further development.[47] Alphapharm's expert has rested his identification of compound (b) as a lead compound on his reading of the '200 Patent and Sohda II.

As described above, the '200 Patent provided protection for TZD derivatives. The molecular structure of compound (b) was illustrated in the patent as one of fifty-four examples of TZD compounds with a certain structure that had been synthesized through steps described in the patent. Examples of still more TZD compounds synthesized through other procedures were also illustrated. The prosecution history of the '200 Patent includes some test results for nine compounds that were presented to the

[46] For ease of reference, certain explanations are repeated here. Pyridyl denotes a six-membered ring of five carbon atoms and one nitrogen atom. The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion.

[47] Alphapharm's Section 355 Statement did not explain why compound (b) would be chosen as a lead compound over others described in either the '200 Patent or Sohda II. Alphapharm has abandoned its assertion in its Section 355 Statement that pioglitazone was obvious based on an analysis of compounds 11 and 14 in Sohda II.

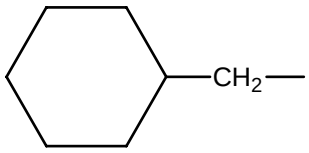
PTO as “typical” of compounds covered by the disclosed invention in order to demonstrate that TZD compounds covered by the invention were “far superior” in their blood glucose and plasma triglyceride lowering effects than compounds in the prior art. Compound (b) was one of the nine whose test results were charted, and it was one of three such compounds charted in the ‘200 Patent that had the best disclosed performance.[48]

Since Takeda only presented test results for nine of the hundreds of millions of TZD compounds covered by the patent application, one with ordinary skill in the art would have had no reasonable basis to conclude that these nine were the best performing of all of the compounds tested by Takeda, and thus that one of these nine should be selected as the lead compound for further development. Even if one could make that leap, however, the prosecution history for the ‘200 Patent disclosed two other compounds, in addition to compound (b), that appeared to have superior performance among the nine that were tested. And, the next year, when Sohda II was published, compound (b) was not singled out as one of the best performing compounds.

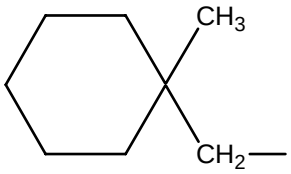
Sohda II, which has also been described above, reported test results on 101 TZD compounds, and identified three that “exhibited the most favorable properties in terms of activity and toxicity.” Each of these three compounds had a different left

[48]Of the nine, three compounds, including compound (b), had a combined score of 7; five had a score of 6; one had a score of 2.

moeity, and therefore, provided different starting points from which one of ordinary skill in the art could make changes in the hope of identifying successful compounds. Compound 47 terminated with an unsubstituted cyclohexane ring[49] and is connected to the rest of the compound by a CH^2. Compound 49, which is ciglitazone, has a similar structure to compound 47, however, there is methyl substituent at the point of attachment to the rest of the compound. Compound 59 is the only one of the three with a pyridyl ring at the left end moeity, however, it is a 3-pyridyl ring. (Pioglitazone's pyridyl ring is a 2-pyridyl ring.[50]) The following diagrams illustrate the differences in the left end of these structures more effectively than a narrative description.



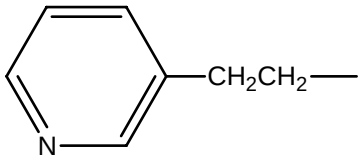
Compound 47



Compound 49

[49] A cyclohexane ring is a saturated ring of six carbons.

[50] The 2-pyridyl is attached to the remainder of the TZD molecule at the second position on the pyridyl ring; the 3-pyridyl, at the third position.



Compound 59

Compound (b) was among the 101 whose test results were reported in Sohda II, but it was not one of the three compounds identified by the authors as having the most favorable performance.

Sohda II gave detailed efficacy data, but did not set out the toxicity test results in comparable chart form. It did discuss in its narrative sections, however, various toxicity and side effect issues which eliminated some of the compounds with strong efficacy ratings from being singled out for their overall performance. For example, seven compounds had the highest combined efficacy score, which was a rating of 7. Sohda II identified problems with toxicity or side effects for six of the seven compounds.[51] Compound (b) was one of the seven, but was described as causing "considerable increases in body weight and brown fat weight."[52] The three compounds that were identified as having the most favorable performance each had a combined efficacy score of only 5.[53]

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[51] The one compound that scored 7 and yet had no identified problems was compound 99. Its structure at the left end moiety differs significantly from the pyridyl.

[52] Compound 3894, which had a combined potency score of five, was described as having the same problematic side effects as compound (b).

[53] Of the 101 compounds in Sohda II, 39 had a combined score of 5 or higher. Twenty-nine of the thirty-nine had been

A person with ordinary skill in the art would had concluded from an examination of the '200 Patent, including its file wrapper, and of Sohda II, that the three compounds identified in Sohda II as promising should be the starting point for further investigation. There were literally thousands of different substituents that one of ordinary skill in the art could consider in modifying those three compounds. Such a person would certainly not have concluded that compound (b) should be chosen as a lead compound over the many other more obvious or at the very least similarly interesting choices presented by that prior art. Indeed, Sohda II teaches away from compound (b) when it specifically comments on its negative effects on body weight and brown fat. Type 2 diabetes is a chronic disease. Any effective drug will be given over a long period of time, and therefore, those of ordinary skill in the art would have been especially sensitive to toxicity and side-effects.

History confirms this analysis. Takeda and another pharmaceutical company worked extensively to develop one of the three compounds identified by Sohda II as particularly promising, before abandoning it because of its toxicity. Ciglitazone was Sohda II's compound 49, and was withdrawn by Takeda from further development during human testing both because it failed the chick lens assay test and due to efficacy concerns.

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described in the '200 Patent.

In fact, because of concerns over toxicity in treating a chronic disease like diabetes, one skilled in the art would have been more likely to choose as a starting point for further research one of the many compounds in Sohda II, and there were over ninety, where the authors did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, than to choose as a starting point a compound with identified adverse effects. If for some yet unexplained reason one chose to start with a compound that had identified problems, one skilled in the art would be motivated to make fairly radical changes to it in order to try to overcome the problems.

Admissions from an Alphapharm scientist confirm that there was no basis to select compound (b) (that is compound 58 from Sohda II) as a lead compound other than hindsight. At his deposition, Rosenberg, who is the head of Alphapharm's intellectual property department and who was also the scientist who formulated its Section 355 Statement, admitted that there was "nothing to recommend" compound (b) over any of the other compounds that had a combined score of 7, and that he only chose compound (b) from Sohda II "because it was similar to pioglitazone."

During his cross-examination, Alphapharm's expert Mosberg presented a new and remarkable explanation for why compound (b) would have been selected as the lead compound by one of ordinary skill in the art over the other six compounds with a rating of 7

and over the three compounds singled out for favorable mention in Sohda II. He argued that it appeared from Sohda II that each of these other compounds, and the molecules closely related to them, were being pursued actively by Takeda and that it would be impractical to compete with Takeda, given its head start, and to invest precious research resources into the compounds Takeda was investigating. This argument was not presented by Mosberg in his direct testimony, where he essentially ignored the existence of the other compounds that scored 7 and the three compounds given prominence in Sohda II. It also directly contradicts his direct testimony, where he asserted that compound (b) would have been selected as a lead compound by one skilled in the art because of the evidence that Takeda was "zeroing in on substituted pyridyl rings."[54]

In any event, there are a myriad of problems with Mosberg's recently invented analysis. First, it is not supported by any intellectually rigorous analysis. Second, the test is not whether a compound seems an unpopular candidate for development among competitors but rather whether one of ordinary skill in the art would have been motivated to choose it as a lead compound in an effort to develop a safe and effective drug to treat diabetes. Third, Mosberg's analysis completely undercuts Alphapharm's

[54] Mosberg's trial testimony also directly contradicts Alphapharm's proposed findings of fact submitted before trial, which indicate that it hoped to establish that one skilled in the art would have understood that Takeda was focusing its attention on compound (b).

contention that compound (b) was the obvious lead compound for investigation. Surely, under Mosberg's revisionist reading of Sohda II, the compounds in which Takeda seemed to be expressing an interest were the more appropriate choices for one skilled in the art who was seeking to find a successful anti-diabetic agent, instead of compound (b), which he believes Takeda had abandoned.

Mosberg also tries to transform its identified problems of an increase in body weight and brown fat into an advantage for compound (b). He argues, with some creativity but little persuasion, that these identified problems would only "motivate one of skill in the art to make changes" in the compound.[55] Such a response does not explain, however, why compound (b), with its associated problems, should be chosen as the lead compound for further investigation.

Mosberg makes two other arguments in an effort to explain why compound (b) would be selected as a lead compound. First, Mosberg argues that further support for focusing on compound (b) comes from the '779 Patent, which specifically claims over sixty compounds including compound (b). Alphapharm's Section 355

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[55] It is undisputed that weight management is an important element in the treatment of Type 2 diabetes and that this was understood in the 1980s. Takeda's expert opines persuasively that the Cunningham Article, which warned that "considerable caution" should used in extrapolating animal studies' brown fat findings to humans, would not have diminished the negative impact of the statements about weight gain in Sohda II on a scientist evaluating compound (b) for exploration. Mylan's Rule 30(b)(6) witness opined that one of ordinary skill in the art would rule out compound (b) as a compound of interest because of its negative profile disclosed in Sohda II.

Statement did not identify the '779 Patent as relevant prior art.

As already described, it was the PTO's initial rejection of the '200 Patent that led Takeda subsequently to file the '605, '779, and '141 divisional patents. Because they are divisional patents, the text of each of the divisional patents is identical to the text of the '200 Patent. The '200 Patent discloses hundreds of millions of TZD compounds. The divisional patents are directed to subsets of those compounds covered by the generic disclosure in the '200 Patent. The '779 Patent, which was filed after the '605 Patent, actually claims a larger class of compounds than the '605 Patent. The '605 Patent claims 1080 compounds, while the '779 Patent claims over one million compounds.[56] These patents claimed not only pyridyl derivatives but also thiazolyl derivatives.

Takeda filed the application for what became the '779 Patent on March 15, 1983, identifying through supporting diagrams over 60 compounds that were TZD derivatives. Essentially, the claims were directed to a structure with a pyridyl or a thiazolyl group at the left end of the TZD molecule, with one to three substituents on those rings, the substituents being selected from lower alkyls, halogens and hydroxyl. Two compounds were specifically claimed, compound (b) and a thiazolyl.[57] Compound (b) was also diagramed as compound 42 on the application. In a

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[56] These numbers do not include the salts and stereoisomers covered by the patents.

[57] The thiazolyl was a 4-methyl 5-thiazolyl.

preliminary amendment of the same date, Takeda stated, "the compounds in which these heterocyclic rings are substituted have become important, especially Compound 42."

There are several problems with Alphapharm's reliance on the '779 Patent.[58] Takeda's expert has given compelling evidence that medicinal chemists do not consider arguments made by patent counsel, particularly when there is contrary information in peer-reviewed literature (such as Sohda II), and that he has never known anyone in his over forty years of work in the field of medicinal chemistry to establish research priorities in this way. Alphapharm's expert essentially agreed, and Alphapharm has presented no evidence to the contrary.[59]

Moreover, if Alphapharm wishes now to rely on a divisional patent as prior art to explain why one skilled in the art would select compound (b) as a lead compound, then it is necessary to consider what one skilled in the art would have concluded by an examination of each of the Takeda TZD patents that had issued by this time. Taken together, they show that Takeda was actively

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[58] Alphapharm may also be attempting to make an inequitable conduct argument concerning the presentation of the toxicity data for compound (b) in the '777 Patent by comparing it to general statements in the '779 Patent about toxicity levels in TZD derivatives. The comparison is spurious and does not require further discussion.

[59] In addition, the file wrapper for the '779 Patent was simply not accessible to one of ordinary skill in the art. As of 1983, patent applications were not prosecuted publicly and the application would not have been available to the public until the patent had issued on April 24, 1984. At that time, the file history would have had to be specially obtained at the patent office.

conducting research in many directions, and had not narrowed its focus to compound (b).

Finally, in support of Alphapharm's argument that compound (b) would have been selected as the lead compound from the prior art, in particular from Sohda II, Mosberg contends that one of ordinary skill in the art would have observed that the four compounds revealed in Sohda II with a pyridyl ring on the left hand side of the structure, display high potency and that of those compounds the compound with the methyl substituent, that is compound (b) or 58, had the highest potency. He points with emphasis to the fact that the substituted pyridyl has a higher combined efficacy score than the unsubstituted pyridyl.[60] From that, Mosberg suggests that one of ordinary skill in the art would have concluded that the methyl substituent was responsible for increasing potency and thus would have been strongly motivated to attempt further substituent replacement to reduce the unwanted side effects of the 6-methyl, while maintaining its potency.

This argument benefits entirely from hindsight. Sohda II describes several clusters of efficacious compounds, including the cluster into which compounds 47 and 49 fall, compounds 47 and 49 being two of the three compounds given particular attention by the authors. In any event, of the cluster into which compound

[60] The unsubstituted 2-pyridyl (compound 57) had a combined score of 5, while the 2-pyridyl with a methyl at the 6 position (compound 58) had a combined score of 7.

(b) falls, the most obvious candidate for a lead compound is the one identified by the article for further investigation, that is compound 59, since the article reported no toxicity or harmful side effects for that compound. Exploration of that compound, which has a 3-pyridyl ring at its left end rather than the 2-pyridyl ring shared by pioglitazone and compound (b), would of course have led in a different direction.[61]

In sum, Alphapharm has failed to show that compound (b) would have been understood by one skilled in the art as a lead compound. There is no support for such a finding based on the prior art that Alphapharm identified in its Section 355 Statement: the '200 Patent and Sohda II. Thus, it now turns to a statement about compound (b) in application for the '779 Patent. One skilled in the art would not have relied on that reference to identify compound (b) as a lead compound given the more exhaustive and reliable scientific analysis presented by Sohda II, which taught away from compound (b), and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 Patent showing that there were many promising, broad avenues for further research.

2) Motivation to Create Pioglitazone

Assuming that compound (b) would have been identified by one skilled in the art as a lead compound, Alphapharm has not shown

[61] At his deposition Mosberg admitted that one skilled in the art would have been led to investigate all of the compounds based on the 2-, 3-, and 4-pyridyl ring, with less emphasis on the 4-pyridyl compounds.

that such a person would have been motivated to synthesize the compounds that had to be created to find pioglitazone. First, one skilled in the art would have done an initial screening of compound (b) for toxicity and concluded that its toxicity made it an extremely poor candidate for modification.[62] The likely course of action at that point, would have been to return to the compounds actually identified in Sohda II as worthy of further research.[63] Second, Alphapharm has failed to point to anything in the prior art that would have presented one skilled in the art with a reasonable expectation of success in creating the compound that became pioglitazone.

Before addressing Alphapharm's specific arguments, it is useful to describe briefly some of the pertinent chemistry and research issues that one skilled in the art would have faced in the 1980s. Many of the tools that assist today in the process of chemical synthesis were not available in the 1980s. At that time, the process of discovering new compounds for pharmaceutical development involved the screening of sample collections, usually those already in the libraries of the pharmaceutical company, or

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[62] As indicated on Table 1 to the '777 Patent, compound (b) was extremely toxic to the liver, heart, and blood.

[63] There is no contention that the investigation of the three compounds identified in Sohda II as worthy of further investigation would have led with sufficient directness to pioglitazone. As already noted, among other things, two did not have a pyridyl ring on the left moiety, and the left moiety in the third was a 3-pyridyl ring rather than the 2-pyridyl ring in the pioglitazone molecule, meaning that its attachment to the remainder of the TZD molecule was from a different point on the pyridine ring.

those created by the chemistry laboratories of the company. When a lead compound was identified, a lead compound being one that contains suggestive properties that are indicative of possibilities for progress, the scientist would modify the lead compound to achieve the right balance of potency and non-toxicity. The modification process was not routine. The chemistry laboratories of the company needed to create, through chemical synthesis, each new compound that needed its potency and toxicity tested. The conceptual acts of moving a methyl substituent to another position on a ring and of replacing it with an ethyl substituent require different starting materials and different chemical processes. While it may be easy to describe in English, the science is time-consuming.

The left-hand end of the TZD molecule is known as a terminating region, and is a so-called hot spot, where small changes can have dramatic repercussions in performance. It would have been a significant research project to understand the consequences of even small modifications to this region of the molecule, and one skilled in the art would not have had any reasonable basis to expect that even small changes in this area would result in an increase as opposed to a decrease in either the efficacy or toxicity of the molecule in any particular organ or body system much less in the body as a whole. There was absolutely no basis whatsoever to form a belief that any particular modification would change a toxic molecule into a non-toxic compound. There was simply no scientific literature which

explained how the particular changes to a molecule that are at issue here would lead to a drug with particular effects, whether for better or worse, in the body. As of the 1980s, and even today, the actual mechanism through which a TZD molecule interacts with the body's processes is not understood. In the 1980s, for instance, scientists did not know the shape of the insulin receptor or the specific molecular target for the TZD compound.

Predicting toxicity based on the structure of a compound is particularly difficult. And, in selecting a lead compound for development of a drug to treat a chronic disease, one skilled in the art would have been particularly sensitive to issues of toxicity. As a result of all of these challenges, it is not uncommon to synthesize thousands of compounds before arriving at a new drug that survives all review and enters the pharmaceutical market in the United States. Alphapharm's expert estimates that, even when one has identified a lead compound, success is achieved in at most 1% of research projects.

Alphapharm's expert, Mosberg, argues that the twin steps of "walking the methyl around the ring" and "homologation" to create an ethyl from a methyl are routine steps in the drug optimization process that would have been performed by one of ordinary skill in the art and would have led quite directly to the discovery of pioglitazone from the investigation of compound (b). Mosberg's opinion was completely undermined by the other evidence presented at trial, including the far more credible testimony from Takeda's

experts. It was also contradicted by Alphapharm's in-house medicinal chemist whose deposition testimony was partially adopted as Rule 30(b)(6) testimony for Alphapharm.[64] Rosenberg testified that in making changes to the pyridyl ring on the left end of the TZD molecule, one would look at a host of substituents, such as chlorides, halides and others, not just methyls. He did not even mention ethyls.

a) Walking the Ring

Nothing in the prior art teaches that changing the position of the methyl substituent on the pyridyl ring could be expected to have a beneficial effect. Indeed, the prior art teaches that the results of a modification like walking a substituent around a ring were highly unpredictable.

Sohda II has only one pyridyl with a methyl substituent, compound 58. There is nothing in Sohda II from which one skilled in the art would conclude that a methyl in a different position on the pyridyl ring would improve efficacy or avoid or reduce compound 58's identified negative side effects.

Mosberg opines that the '200 Patent teaches that walking a substituent around the ring was a process "known" to Takeda. Many common (as well as sophisticated) chemical processes were no doubt known to Takeda; that is beside the point. The issue is

[64] Alphapharm had identified Rosenberg as one of its trial experts, and had served his expert report. After he was deposed, however, Alphapharm withdrew its offer of Rosenberg as an expert at trial. Before making that decision, Alphapharm had adopted portions of Rosenberg's deposition testimony as evidence given by Alphapharm pursuant to Rule 30(b)(6), Fed. R. Civ. P.

whether there was any ground for a reasonable expectation of success that can be located in the prior art by a person of ordinary skill to choose a particular process to achieve the desired goal.

Mosberg gives three sets of examples[65] from the illustrations in the '200 Patent that show either a methoxy (CH_3O) or a chloro (CI) being "walked around" a different ring, a benzene ring.[66] He does not assert, however, that any of the disclosed results from that process taught that such a process would be likely to lead to any success, or that any particular position on a ring was likely to more efficacious or less toxic than any other. None of the three examples includes a substituent at the 5th position on the ring, where pioglitazone's substituent is located.

An examination of the efficacy data from Sohda II for the phenyl compounds to which Mosberg points suggests that substituents in a lower ring position may be more potent, principally by comparing the efficacy scores for substituents in the 4th position with those in the 2nd position.[67] Alphapharm has

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[65] Mosberg discusses compounds 1 and 2; compounds 18 and 19; and compounds 31, 32 and 33 from the '200 Patent. In Sohda II, these are compounds 32 and 31; compounds 13 and 12; and compounds 5, 4, and 3, respectively.

[66] A benzene ring, in contrast to a pyridyl ring, does not have a nitrogen atom. A compound with a benzene ring is referred to as a phenyl.

[67] Alphapharm did not make this comparison or argument at trial.

not shown, however, that one skilled in the art would have understood that these results were transferable from a phenyl to a pyridyl compound, that they would pertain to a comparison between a substituent in the 6th and 5th positions, or that they would eliminate toxicity.

Mosberg argues that Takeda's historical experience confirms his opinion that it was expected that one would simply walk the methyl around the ring. This is, of course, an improper use of hindsight. Nonetheless, Takeda's historical experience is directly to the contrary. Compounds (c), (d) and (e) were each first synthesized in 1983; pioglitazone was first synthesized in 1982. Takeda clearly did not move from compound (b), which had been synthesized in 1978, to pioglitazone by "walking the ring."

Even if Takeda had moved away from compound (b) by "walking the ring," it would have discovered significant toxicity problems as soon as it synthesized and then tested each of the other methyl substituents on the 2-pyridyl ring. As illustrated in Table 1, compounds (d) and (e) each have significant toxicity. Compound (c) failed the chick lens assay screening. In sum, Alphapharm has not shown that one skilled in the art would have been motivated to move to pioglitazone by "walking the ring."

b) Homologation

Alphapharm has no more success with its argument that one skilled in the art would have been led to create a homolog of a

methyl substituent on the 2-pyridyl ring,[68] than it did with its ring-walking argument. Alphapharm has failed to show that the prior art would have invested in a person with ordinary skill in the art a reasonable expectation that the substitution of an ethyl for an methyl would lead to beneficial results.

Sohda II describes over a score of compounds with a methyl substituent and eight compounds with an ethyl substituent. There is no discernable pattern of biological activity associated in a comparison of the two substituents in the prior art. Nothing in the prior art suggests that the process of substituting an ethyl for a methyl would be of any more assistance than using any other of the many possible substituents or changing course entirely and adopting a base structure other than the 2-pyridyl ring.

Indeed, Alphapharm has not identified any basis to find that even those with great skill understood in the 1980's (or even today) that the substitution of an ethyl group for a methyl group is likely to have a beneficial effect on biological processes. Our understanding of the biological properties of compounds is too rudimentary even today to allow us to form reasonable expectations regarding such a result.

In particular, Alphapharm is confronted again with the significant hurdle placed by the toxicity found in compound (b). Having found such high levels of toxicity to the heart, liver,

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[68] As noted earlier in this Opinion, a homolog is a chemical structure that differs from the parent compound by a single, constant increment of one carbon (and associated hydrogen atoms), such as adding a methyl group.

and blood cells in compound (b), it has not pointed to anything in the prior art that would suggest that creating a homolog of the compound would be likely to reduce much less eliminate toxicity, either in any particular body system or as a whole.[69]

Ignoring entirely the substantial issue of compound (b)'s toxicity, Mosberg asserts that Sohda II teaches that the substitution of a methyl increases potency, and specifically that a comparison of Compounds 57 and 58 in Sohda II demonstrates that homologation increased the efficacy of pyridine compounds. Compound 57 is the unsubstituted pyridine ring; compound 58 is compound (b) (the 6-methyl on the pyridine ring).[70]

A more straightforward reading of Sohda II indicates that its authors understood that homologation does not ameliorate toxicity. The Sohda II authors point out that "[a]lthough compounds 56, 57, 58, 59 and 63 in Table IV showed potent activities, they, especially 57 and 58, caused considerable increases in body weight and brown fat weight." (Emphasis added.) One of ordinary skill in the art would therefore have been more likely to conclude from Sohda II that homologation had no

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[69] If one of ordinary skill in the art were confronted with toxicity issues, she would be "well-advised," according to Danishefsky, to try substituents that would change significantly the dipole moment of the molecule, that is the electron density of the compound. Examples of such substituents do not include an ethyl, and do include methoxies, alcohols, and halides, among many others.

[70] Compounds 57 and 58 were reported in Sohda II to have the same effect on hypoglycemic activity (a score of 3), while compound 57 scored 2 and compound 58 scored 4 with respect to plasma triglyceride-lowering activity.

tendency to decrease unwanted side effects and to focus research efforts elsewhere. There were other compounds described in Sohda II as efficacious as compound 58, including one with no identified side effects or toxicity. And, as already noted, the authors of Sohda II recommended investigation of three other compounds, not compound 58.

Mosberg argues that the '200 and '779 Patents teach that Takeda "may" prefer to use the lower alkyls[71] and in particular a methyl (CH_3) or an ethyl (C_2H_5) as substituents, and therefore it would not be surprising if Takeda used an ethyl substituent on a pyridyl ring. He relies on the Nohara Article and Sohda II as evidence that homologation was routine at Takeda. The test, of course, is not what Takeda might have tried, but whether one skilled in the art would have a reasonable expectation of success from synthesizing the homolog.

In any event, nothing in the '200 and the '779 Patents, or in any other publication from Takeda, would have given one skilled in the art an expectation of success from the substitution of an ethyl for a methyl. In its patents, Takeda specifically claims a variety of substituents on identified systems. For example, the '779 Patent includes substituents on a pyridyl or thiazolyl group, noting that "[a]s examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl,

[71] Alkyls are linear chains of carbon atoms singly bonded to other carbon atoms or hydrogen atoms.

etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.) and hydroxyl."

Finally, Mosberg points to specific illustrations in the '200 Patent that demonstrate to him that Takeda was aware that the substitution of a methyl with an ethyl "should be carried out to test for useful compounds." Again, this is not an opinion that there was any reasonable basis for an expectation of success. In any event, when the specific illustrations selected by Mosberg are actually examined, using the efficacy data on those same compounds as provided by Sohda II,[72] it is immediately apparent that the prior art did not teach that the substitution of an ethyl for a methyl was likely to be beneficial. Sohda II shows a higher combined efficacy score for the methyl over the ethyl for one set, and an identical combined score for the methyl and the ethyl in the second set. The third set in the '200 Patent includes five compounds, but only three of the five are discussed in Sohda II. This set is a homologous series, with a CH_2 component repeatedly added. The Sohda II efficacy scores show no pattern, however, from the addition of the carbon atom.[73]

The position taken by Alphapharm's expert is perhaps best captured by his annotations to the expert report of Takeda's

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[72] Mosberg cites to three sets of examples in the '200 Patent: compounds 3 and 4; compounds 5 through 9; and compounds 15 and 16. In Sohda II, these are compounds 36 and 37; 38 to 40 (only three of the five are reported in Sohda II); and 11 and 14.

[73] The compound in the middle of the series has the highest score.

expert Danishefsky. On that report, he wrote in the margin that he agreed that a review of the biological effects of various substituents, as disclosed in the Sohda II article, made it clear that biological activity is "unpredictable." He added, "but this does not in [any]way make the choice of such analogs less obvious to try."[74] The test, of course, is not whether it is "obvious to try" the synthesis of a particular compound, see, e.g., In re O'Farrell, 853 F.2d 894, 902 (Fed. Cir. 1988), but whether one skilled in the art would have a reasonable expectation of success from doing so. At trial, the best the expert for Alphapharm could offer is that essentially anything can happen when one modifies a compound, so a change for the better might happen, and if it did, it would not be surprising. This does not come any closer to articulating a reasonable expectation of success.

In summation, Alphapharm's counsel tried with no success to limit the damage done by its expert's testimony. Admitting that there is inherent variability in the biological effects produced from even small changes in the structure of chemical compounds, he argued that a variation in the degree of an effect is entirely

[74] Additional annotations by Mosberg indicate that he did not believe that there was any reasonable expectation of success from any particular modification of the molecule. He agreed that "there is no data or information to even suggest that substitution of an ethyl for a methyl substituent would lead to predictable improvements in blood glucose or triglyceride lowering activity." Mosberg added in the margin, "there is no predictability only logical choice of analogs to try." As a final example, Mosberg notes in another annotation, that an effect on toxicity from small structural changes "can be neither expected nor unexpected. It would not be surprising."

expected and is not surprising. He suggested that what would be surprising was to find an effect from the small change in the composition of a molecule in an entirely different body organ or system. Again, the issue is not whether something would be surprising, although the discovery that pioglitazone was non-toxic certainly qualifies as a surprising and unexpected event, but whether one could reasonably expect success.

In sum, even if compound (b) could have been identified by one skilled in the art as a lead compound worthy of further investigation, Alphapharm has failed to show that such a person would have had a reasonable expectation of success in synthesizing the pioglitazone molecule. Alphapharm has not shown that pioglitazone was prime facie obvious.

D. Objective Indicia of Non-Obviousness

1) Unexpected Results

Given Alphapharm's failure to show prima facie obviousness, there is no need for an extended discussion of the objective factors used to evaluate obviousness. For reasons already described, pioglitazone's non-toxicity was entirely unexpected. Compound (b) was a highly toxic compound, and nothing in the prior art would have led one skilled in the art to expect that the 5-ethyl on a 2-pyridyl ring would be non-toxic. As Alphapharm's Rosenberg admitted at his deposition, pioglitazone is "clearly superior" to compound (b) because of its non-toxicity.

There is one evidentiary issue that arose in connection with the issue of unexpected results that requires some discussion. Alphapharm offered evidence at trial that a long-term study of the effect of pioglitazone in dogs, conducted by Upjohn after Takeda had applied for what became the '777 Patent, suggested that pioglitazone may lead to an increase in heart size, and thus has some toxicity. An Upjohn scientist who testified at trial discounted that interpretation of the test results. It is unnecessary to make any findings regarding this evidence, however, since it is entirely irrelevant to the issue of whether pioglitazone's non-toxicity, as disclosed in the '777 Patent, was an unexpected result.

Pioglitazone has, of course, been approved by the FDA and the defendants challenge Takeda's patent because they believe it is an effective and non-toxic drug that will be profitable for them to sell. As significantly, while it may be appropriate to use later-acquired evidence to bolster a finding of unexpected results,[75] to illustrate for instance that an invention is even more beneficial to mankind than was originally understood, see Knoll Pharm. Co. v. Teva Pharm. Co., 367 F.3d 1381, 1385 (Fed. Cir. 2004), it is another thing altogether to suggest that after-acquired evidence should be used to undercut what appeared at the time of the patent application to be unexpected results. For

[75] There is, for example, strong evidence that the scientific community has come to understand that pioglitazone has a measurable and unexpected advantage over the other TZD on the U.S. market.

instance, it would be entirely unfair to the patent applicant to discount what appeared at the time of an application to be unexpected results because our advancing and improved scientific knowledge allows us to understand why such results are to be expected. Therefore, as with all objective factors used to analyze the obviousness issue, after-acquired evidence of unexpected results should not be used to undermine a patent without a careful analysis of relevance. Here, the Upjohn tests, conducted long after the application for the '777 Patent, are irrelevant.

2) Additional Secondary Considerations

Evidence concerning other objective factors also shows that pioglitazone was a non-obvious invention. First of all, it is a huge commercial success. ACTOS® was launched in 1999, and by 2003 held 47% of the TZD market, as well as 9.9% of the total OAD market. In 2003, the gross sales of ACTOS® exceeded $1.7 billion. ACTOS® is the embodiment of pioglitazone, the invention disclosed in the '777 Patent, and therefore this commercial success can presumptively be attributed to the invention itself.

Pioglitazone also responds to a long felt but unmet need in the market of pharmaceutical treatments of diabetes. The introduction of TZDs, led by Rezulin® in 1997, revolutionized the care of diabetes. Rezulin®, however, has been removed from the U.S. market due to issues associated with liver toxicity, and today, only ACTOS® and Avandia® are available. Out of the

millions of TZDs, only these two have been found to be safe and effective to treat insulin resistance in the muscle.

Alphapharm presents several arguments in a futile effort to undermine Takeda's compelling objective evidence of non-obviousness, particularly its evidence of commercial success. While Alphapharm concedes that there is evidence both of commercial success and that the successful product is claimed in the patent, it argues that other factors serve to undercut "the prima facie case of nexus" between the commercial success and the claimed invention.

Alphapharm argues that much of the commercial success of ACTOS® is due to events that were unforeseen at the time that the '777 Patent issued, such as the withdrawal of Rezulin® from the market, and an unexpected rise in obesity with an accompanying increase in the incidence of diabetes.[76] These arguments miss the mark. There is no requirement that the invention be the only successful product in its market niche or the most successful. Moreover, ACTOS® would have been an important and successful invention by any reasonable measure even if the incidence of diabetes had remained unchanged since the time of the invention.

Alphapharm also argues that Takeda's success is more attributable to its marketing efforts, particularly its partnership with Eli Lilly, than the inherent value of the

[76]There is no need to explore the extent to which the perceived rise in obesity and diabetes is due to a redefinition of obesity in 1998, and a change in the diagnostics for diabetes in 1997.

invention. This argument flies in the face of the strong evidence from medical practitioners about the benefits and the perceived benefits of ACTOS®. In any event, Takeda and GlaxoSmithKline invest roughly the same amount of money in their efforts to market their two TZD products, and both drugs have found success.

Finally, Alphapharm argues that Takeda's prior art patents, particularly the '200 and '605 Patents, undermine the nexus between ACTOS®'commercial success and the non-obviousness of the '777 Patent. The suggestion is that because Takeda had the right to exclude others from making the closest prior art compounds, the ability of other companies to enter the TZD market was stifled.[77] The argument is completely specious. Alphapharm has not shown that any of the compounds disclosed by Takeda in its patents were viable candidates for commercial development. Takeda's competitors had every opportunity to develop new compounds that were improvements over the compounds Takeda disclosed. This is exactly what Sankyo did in developing troglitazone, the active ingredient in Rezulin®. The patent that protects troglitazone lists the '605 and '902 Patents as prior

[77] In making this argument, Alphapharm relies on Merck, 395 F.3d at 1377, but in doing so, reads the case far too broadly. In Merck the patent at issue was a method claim for the use of a particular compound, which was protected by a patent owned by Merck. Id. at 1366. Because Merck owned the underlying patent, and thus could prevent others from commercially developing the method of use at issue, the court found that the "chain of inferences fails on these facts." Id. at 1377. The case does not establish that commercial success is not probative simply because a patent holder also holds a prior art patent.

art. The fact that only one other company has a TZD in the market today, despite the commercial opportunities available for an effective insulin sensitizer, is strong secondary evidence of pioglitazone's non-obviousness.

In sum, Alphapharm has not carried its burden of showing that the invention of pioglitazone was obvious. It has searched for a theory of obviousness, and its efforts have proven futile with each iteration of a theory.[78] Alphapharm's Section 355 Statement did not articulate a successful theory of obviousness, and its efforts to create one through the direct testimony of its expert, and yet another one as the trial unfolded all failed. Nothing in the prior art would have given one skilled in the art any reasonable expectation that the creation of pioglitazone would result in the discovery of an anti-diabetic treatment that was efficacious and non-toxic.

II. Inequitable Conduct

Mylan contends that the '777 Patent is invalid because Takeda engaged in inequitable conduct. Applicants for patents are bound by a duty of "candor and good faith" to the PTO. Purdue Pharma L.P. v. Endo Pharm. Inc., 04-1189, 04-1347, 04-

[78] It is telling that two of the defendants never sought to attack the '777 Patent on the ground that it was obvious, and a third defendant abandoned the theory of obviousness it had articulated in its own Section 355 Statement.

1357, 2006 WL 231480, at *4 (Fed. Cir. Feb. 1, 2006).[79] Included in the duty is the obligation of applicants to disclose information of which they are aware that is "material to the examination of the application." 37 C.F.R. § 1.56(a) (1985).

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[79] The conduct of applicants while applying for patents is governed by 37 C.F.R. § 1.56 ("Rule 56"), which is promulgated by the PTO pursuant to 35 U.S.C. §§ 6 and 131. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1179 n.8 (Fed. Cir. 1995). The governing standard for evaluating defendant Mylan's claims of inequitable conduct is the regulation as it stood in 1986, when Takeda pursued its application for the invention covered by the '777 Patent. See id. In 1986, the regulation read in relevant part:

> (a) A duty of candor and good faith toward the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to the examination of the application. Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. The duty is commensurate with the degree of involvement in the preparation or prosecution of the application.
>
> (d) No patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence. The claims in an application shall be rejected if upon examination pursuant to 35 U.S.C. 131 and 132 [sic], it is established by clear and convincing evidence (1) that any fraud was practiced or attempted on the Office in connection with the application, or in connection with any previous application upon which the application relies, or (2) that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the application, or in connection with any previous application upon which the application relies.

37 C.F.R. § 1.56 (a), (d) (1985) (emphasis supplied).

The duty encompasses an "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information." Purdue Pharma, 2006 WL 231480, at *4. Materiality and intent "must be shown by clear and convincing evidence." Id. The burden of proof required to prove inequitable conduct has been described as a "heavy burden". Hoffman-La Roche, Inc. v. Promega Corporation, 323 F.3d 1354, 1359 (Fed. Cir. 2003)

For patents prosecuted before 1992, "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application as a patent." 37 C.F.R. § 1.56 (a); see Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1365 (Fed. Cir. 2003). Materiality is not limited to matters reflected in the claims of the patent, PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1322 (Fed. Cir. 2000), but embraces "any information that a reasonable examiner would substantially likely [sic] consider important in deciding whether to allow an application to issue as a patent." Dayco Products, 329 F.3d at 1368 (citation omitted); see Akron Polymer Container Corp. v. Exxel Container, Inc., 148 F.3d 1380, 1382 (Fed. Cir. 1998). The standard for materiality is not a "but for" standard. Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989); see also Digital Control Inc. v. Charles Mach. Works, 05-1128, 2006 WL 288075, at *7 (Fed. Cir. Feb. 8, 2006). It is not necessary to find that an examiner

relied on the misrepresentation or omission at issue, only that it would have been "within a reasonable examiner's realm of consideration." Hoffman-La Roche, Inc., 323 F.3d at 1368 (citing Merck & Co., 873 F.2d at 1421). Affidavits submitted to the PTO may be "inherently material." Digital Control, 2006 WL 288075, at *8; see also, Refac Intern., Ltd. v. Lotus Development Corp., 81 F.3d 1576, 1583 (Fed. Cir. 1996).

Direct evidence of intent to deceive is "rarely available", but intent "may be inferred from clear and convincing evidence of the surrounding circumstances." Purdue Pharma, 2006 WL 231480, at *9 (citation omitted); see also Ferring B.V. v. Barr Labs., Inc., 05-1284, 2006 WL 335601, at *8 (Fed. Cir. Feb. 15, 2006). While a "court must weigh all evidence, including evidence of good faith" in determining intent, "a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." Purdue Pharma, 2006 WL 231480, at *9 (citation omitted).

If the duty is breached in a way that is both material and intentional, then the patent will be invalidated if "the equities warrant a conclusion that inequitable conduct occurred." Id. at *4. The material misrepresentations or omissions must be "sufficiently serious in light of the evidence of intent to deceive, under all the circumstances, to warrant the severe

sanction of holding the patent unenforceable." Hoffman-La Roche, 323 F.3d at 1372.

Mylan has failed to carry its heavy burden of showing that Takeda engaged in inequitable conduct. Mylan principally claims that Takeda intentionally made material misrepresentations in its presentation of the comparative test results for the six compounds listed in Table 1 of the '777 Patent, and that Takeda should have added information concerning a seventh compound to the table.

There are many indicia of Takeda's good faith in its application to the PTO in 1986. First, with the exception of two test results it obtained in response to the Office Action, the test results Takeda presented to the PTO in Table 1 were drawn from reports that Takeda and its research partner Upjohn had used in 1984 to select five compounds, including pioglitazone, for further research and potential development as a pharmaceutical. Takeda had every incentive to reflect in those reports its best judgment about what the test results showed so that the companies' money and the scientists' energies would be spent as productively as possible. There is simply no basis to find that there was any misrepresentation in the 1984 reports, much less any incentive to misrepresent test data.

Second, Takeda identified the relevant prior art to the PTO. Both Sohda II and the '200 Patent were described. In addition, the chemical structure for the closest prior art –- compound (b) on Table 1, which is compound 58 in Sohda II -- is set out in a

diagram so that it can be easily compared to the chemical structure for pioglitazone and the other compounds listed in Table 1.

Third, Takeda did not manipulate the data presented in Table 1 to make pioglitazone appear better than its internal data reflected. For example, Table 1 shows that compound (b) is superior to pioglitazone in the reduction of both blood glucose and triglycerides. Even when the Office Action required Takeda to fill in three more data points in Table 1 –- the triglyceride data for rats for compounds (c), (d) and (e) –- Takeda gave the PTO figures that were comparable to or superior to the figures for pioglitazone in Table 1.[80]

Fourth, Takeda had powerful additional evidence of the superiority of pioglitazone over the prior art which it did not present to the PTO. Report A-15-34 reflects the results of the in vitro chick lens assay[81] for many compounds, including those in Table 1. Only pioglitazone and compound (e) of the six compounds listed in Table 1 showed no evidence of toxicity in this test. This was additional evidence of the superiority of pioglitazone over the compound in the prior art to which it was most structurally similar, compound (b), which Takeda had at hand to share with the PTO if necessary.

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[80] Pioglitazone ED^{25} value for lowering rat triglyceride levels was shown as 3; the comparable values for compounds (c), (d) and (e) were reported as 6, 4 and 2, respectively.

[81] It was this test which had resulted in the abandonment of ciglitazone as a marketable pharmaceutical.

Fifth, there is no dispute about the superiority of pioglitazone over compound (b), the only prior art compound in Table 1. Mylan cannot explain how Takeda could have anticipated in 1984, when it created Reports A-15-13 and A-15-34, that information about compounds (c), (d) or (e) would be included in the PTO application or what additional explanations the examiner would seek in an Office Action.

Ignoring this powerful evidence that Takeda acted in good faith in its presentation to the PTO, Mylan has cobbled together a series of arguments in an effort to show inequitable conduct. As noted, its arguments relate to the presentation of data in Table 1. It emphasizes data concerning two compounds: compound (c), which is the 5-methyl homolog of pioglitazone, and compound 3894, which is the unsubstituted pyridyl ring. With respect to compound (c), Mylan contends that Takeda misrepresented the data regarding compound (c)'s potency to make it appear weaker than pioglitazone. It points out that compound (c) had no toxicity indicated on Table 1, and therefore, pioglitazone would not have appeared superior to compound (c) if their efficacy numbers were presented as comparable.[82] With respect to compound 3894, Mylan argues that Takeda had a duty to report the comparative test results for this compound on Table 1, but did not. Compound 3894 had comparable if not better efficacy than pioglitazone, but was rejected for development by Takeda due to its toxicity to the

[82] Compound (c) failed the chick lens assay test, but those data were not presented to the PTO.

heart. In addition, as described below, Mylan raises a few other issues to attack Taeda's honesty in its presentation of Table 1 data.

Before addressing Mylan's categories of alleged misrepresentations, a few observations are in order. Many of Mylan's examples of the misrepresentation or omission of data rest on testing data it culled from surviving Takeda notebooks that were produced in discovery in 2004 and 2005. The screening tests were conducted approximately 20 years earlier, and not all of Takeda's laboratory notebooks have survived. Thus, Mylan's analysis rests on the fallacy that it has a complete set of the testing data from which to judge the completeness and fairness of the presentation of the testing results to the PTO.

There is a second flaw in Mylan's contention that Takeda should have used the experimental data lifted directly from the notebooks rather than the data in the reports on which Takeda and Upjohn relied to make their research decisions. Presenting raw, unanalyzed data from notebooks would have been both incomprehensible to an examiner and misleading. Indeed, the notebooks contain some test results for pioglitazone that are more favorable than those listed on Table 1 and test results for some of the other compounds that are less favorable than the descriptions of those compounds on Table 1.

Fujita analyzed all of the test results in 1984, and chose to include in Report A-15-34 those that he considered the most reliable. Takeda and Upjohn relied upon the data in that report

in making critical business decisions, and it was entirely appropriate for Takeda to rely on that same data in preparing Table 1 for the PTO.

With two exceptions, which are discussed below and concern the strain and age of rats, Mylan has failed to show that there was any misrepresentation or material omission in Takeda's presentation of data. With respect to the two errors, Mylan has failed to show that the errors were either material or the result of any intentional misconduct by Takeda.

A discussion of Mylan's specific contentions follows. Its contentions are organized according to the column in Table 1 to which they relate. Its arguments concerning compound 3894 –- the compound not included on Table 1 -- are addressed last.

A. Misrepresentations

1) Mouse ED^{25} values

Mylan argues that most of the ED^{25} values for the lowering of blood glucose and plasma triglycerides in mice that were reported in Table 1 were false and misleading, and that the actual test results obtained by Takeda were not reported to the PTO. In particular, Mylan stresses data obtained in a single 1983 experiment in which pioglitazone and compound (c) were tested together or head to head,[83] and shown to have roughly the

[83] Mylan makes a similar argument for compound (e), claiming that data from a single experiment in a Takeda notebook shows that compound (e) outperformed pioglitazone. For the reasons discussed in the analysis of the argument concerning compound (c), Mylan has not shown that a misrepresentation occurred in the presentation of the ED^{25} mice data on Table 1.

same ED^{25} values, while Table 1 reflects pioglitazone significantly outperforming compound (c) in these measures.[84]

As already noted, the ED^{25} mouse data in Table 1 is identical to that contained in Report A-15-34. Mylan's assertion that there was a misrepresentation is based exclusively on the results of a handful of experiments Mylan located in surviving Takeda notebooks. There were many more experiments conducted by Takeda than are reflected in the surviving notebooks. Indeed, as has been explained previously, because there were so many screening tests performed, for many compounds Report A-15-34 presents a range of test results for the efficacy testing. It first lists the figure which Fujita selected as the most reliable, and then in parentheticals gives a range of test results.[85]

It was entirely appropriate, and indeed necessary, for Fujita to apply his professional judgment to the mass of test results and select the test results on which he felt that Takeda and Upjohn could best rely in the Fall of 1984. Not all tests

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[84] Table 1 showed ED^{25} blood glucose and triglyceride lowering scores of 6 and 6 for pioglitazone, but 20 and 20 for compound (c). In the single experiment to which Mylan points, the comparable pioglitazone values were 5.2 and 14, but 6.4 and 18 for compound (c).

[85] For instance, the ED^{25} blood glucose data for compound (c) were reflected in Report A-15-34 as: "20 (2-5)". The data in the parenthetical represent the relative potency of compound (c) to ciglitazone, ciglitazone being accorded a rating of one. Fujita chose the test reflecting an ED^{25} value of 20 as the most reliable test, but by including the data in the parenthetical, reflected that the test results ranged from values between 8 and 20. Ciglitazone had an ED^{25} value of 40 in Report A-15-34.

yield similarly reliable data. Some of the test results from the Takeda notebooks on which Mylan has relied are preliminary two dose tests, which would not yield reliable ED^{25} data. In other tests it appears that the effective dose is beyond the administered doses, and again would not be a reliable basis for determining the effective dose. In other surviving tests, where there does not appear to be any particular defect in the test, Mylan still has not shown that those data should have been used in Table 1 instead of the data Takeda chose to present there.[86] Without having all of the underlying test results from which Fujita selected the most reliable tests to calculate the ED^{25} values contained in Report A-15-34, it is simply impossible today to reconstruct why any single test was or was not chosen as the most reliable. What can be established today with confidence, however, is that Fujita had every motive to use his best judgment in 1984 in compiling the data for Report A-15-34, and it was those data which were presented to the PTO in 1986.

In this connection it is important to note that Takeda had given over fifty compounds to Upjohn, as well as KKA^{y} mice, so that Upjohn could replicate the efficacy testing that Takeda was

[86] Using the notebook data to create ED^{25} values, and after eliminating tests where only two doses were administered or where the dose response curve was flat (indicating that the ED^{25} value was beyond the range of doses tested), the data currently available results in an identical ranking of pioglitazone, and compounds (a) and (c) to that presented to the PTO: pioglitazone was superior to compound (c); compound (a) had the poorest performance. There was insufficient surviving data for the other compounds to do a meaningful comparison.

doing in its own laboratories. Two scientists who were deeply involved in the 1984 diabetes drug program at Upjohn testified at trial and confirmed that Upjohn not only did its own efficacy testing but also that all of the results it obtained were consistent with the results that Takeda reported. These two scientists, neither of whom has any stake in this litigation, spoke highly of the competence and integrity of the Takeda scientists and its testing program. The existence of Upjohn's parallel testing program is yet another reason to find that Fujita used his best judgment in choosing the efficacy numbers (and other data) for Report A-15-34. Upjohn's scientists were in a position to disagree with his presentation of the data, and Fujita knew that.[87]

There are two additional arguments that Mylan makes about the presentation of the efficacy scores in Table 1 for mice. It points to comparisons with ciglitazone that were contained in monthly internal reports at Takeda in early 1984, and Report A-15-13, circulated in February 1984. These comparisons listed

[87]In a chapter of a book published in 1990, the Upjohn scientists who testified at trial described research into ciglitazone, pioglitazone and other TZDs. They reported that Takeda discovered through its research that replacing the left hand moeity of ciglitazone with a 2-pyridinylethoxy produced compounds "approximately 5-10 times more potent than ciglitazone". They added that further testing of the compounds for efficacy and safety resulted in the selection of pioglitazone for development. Despite Mylan's arguments to the contrary, nothing in this general description of the Takeda screening program undermines the reliability of Report A-15-34, a report on which these same Upjohn scientists relied to make research decisions.

compounds that screening tests had determined were “five times as potent as ciglitazone.” Pioglitazone and compound (c) were among the compounds found as having such a superior performance. Mylan argues that it is inconsistent to identify compound (c) as five times more potent than ciglitazone in these internal documents, and yet to list it on Table 1 as only two times as potent.[88]

Takeda’s early screening tests were part of a program to find more potent and less toxic compounds than ciglitazone. They created new compounds, including compounds (c), (d) and (e) in mid-1983, and subjected them initially to two-dose tests, and those that survived that screening, to three-dose tests. During 1984, Takeda continued to test compounds. For the reasons already explained, there is no reason to doubt that Takeda used its best judgment in selecting the most reliable potency values for Report A-15-34 from among the universe of available test results,[89] and those same numbers appear in Table 1. Mylan has not shown that Takeda engaged in inequitable conduct by failing to give the PTO data reflecting the best performance by a compound, instead of the performance judged by extremely well

[88] On Table 1, ciglitazone’s ED_{25} values for lowering blood glucose and triglyceride levels in mice are both 40, while compound (c)’s are listed as 20.

[89] As already noted, Report A-15-34 did include a range of potency, comparing each compound’s potency to ciglitazone, and compound (c)’s range of potency was listed in Report A-15-34 as “2-5" or two to five times as potent as ciglitazone.

qualified scientists as the most reliable performance.[90]

Finally, Mylan finds in another section of Report A-15-34 support for its argument that Table 1 was misleading. In Figures 5 and 6 of Report A-15-34, pioglitazone is shown as somewhat more potent in mice, and as creating less "brown fat" in rats, than compound (c).[91] Pioglitazone is not shown in these figures, as it is in Table 1 of Report A-15-34 (and in Table 1 of the patent), as over three times more potent than compound (c). Takeda apparently chose to use some of the test results for compound (c) in these figures that were different from the values it chose as the most reliable when it created Table 1 of Report A-15-34.

Mylan has not shown that Takeda should have presented the data used to create the two figures in Report A-15-34 instead of the Table 1 data to the PTO. The two figures do not even have numbers associated with a particular compound; the figures are simply graphs composed of points entered on a logarithmic scale. One can only estimate, and very roughly at that, what the

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[90] Mylan has argued that Takeda should have given the PTO the range of test results reflected in the parentheticals in Report A-15-34. Mylan has not shown that the range of results would have been material to the examiner or anything other than an additional layer of detail that was unnecessary for the examiner to perform his function. Giving the PTO the most reliable test data, as opposed to a summary of all test results was sufficient to meet Takeda's obligations to the PTO.

[91] Takeda created a graph of the data using these two parameters and from that graph formed the hypothesis that the increase in the brown adipose tissue ("brown fat") in the rats may be partially due to the pharmacological potency of a compound.

underlying values are. The only reliable numbers in Report A-15-34 are those that were reported to the PTO.

Takeda's testing, which was extensive, was nonetheless preliminary, screening testing, used to identify a small group of compounds, ultimately five, for more intensive testing and potential development. Takeda was under no obligation to conduct more extensive testing before applying for a patent; its only obligation was to present its results as of that time honestly. Mylan has not shown that Takeda violated that obligation in connection with the mouse efficacy data.

2) Rat ED^{25} values

Mylan argues that some of the ED^{25} values for plasma triglyceride lowering that Takeda obtained from testing rats were not obtained in the manner Takeda described to the PTO in the '777 Patent application and the Amendment, and that Takeda concealed some of the results it did obtain from its testing.[92] Mylan makes three separate arguments, but has not shown in connection with any of them that Takeda engaged in inequitable conduct.

a) ED^{25} value for pioglitazone

Relying again on surviving notebook data, Mylan argues that Takeda misrepresented the ED^{25} in rats for pioglitazone. Table 1 reported the value as 3 for pioglitazone, but Mylan points to

[92] In its summation, Mylan only mentioned one of these three issues: the failure to tell the PTO that a control animal had been excluded from an experiment.

data from tests reflected in surviving notebooks that show different values, one of them lower than a 3.[93] For the reasons already discussed, Mylan has not shown that there was any misrepresentation by Takeda. Takeda took the figure for pioglitazone from Report A-15-34, and that was a reliable source of data to present to the PTO.

b) Exclusion of a control animal

Mylan argues that Takeda misrepresented its testing protocol to the PTO when it indicated that there were five rats in each testing group, including the group of animals used as a control. Mylan argues that Takeda should have advised the PTO that in one test it had omitted test data obtained from one control animal.[94]

In responding to the Office Action, Takeda conducted experiments to obtain ED^{25} values for plasma triglyceride lowering in rats for compounds (c), (d) and (e). One of the five animals in the control group gained comparatively little weight during the test period and had anomalous readings for other pertinent characteristics.[95] In averaging the data obtained from

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[93] The ED^{25} values identified by Mylan for pioglitazone are 17.9, 7.8 and 2.3.

[94] Mylan initially argued that Takeda should not have eliminated the control animal from its calculations since the censoring of the animal dramatically altered the test results. It appears to have abandoned this argument. As explained above, the censoring was entirely appropriate.

[95] The control animal had an elevated NEFA level (non-esterified fatty acids), which indicated that it was either not sufficiently eating or assimilating its food.

the control group in this test, a Takeda researcher chose to eliminate the readings from this one animal.

The “censoring” of animals in biological testing is encouraged where results are not representative and where inclusion would be misleading. The exclusion of one control animal was entirely appropriate here and reflects the exercise of sound scientific judgment. Scientific publications do not always report the exclusion of one laboratory animal in their description of test results, and there is no basis to find that it should have been reported to the PTO or that the test results should have included the readings obtained from this single animal.

Mylan also argues that Takeda’s statement in the Amendment about control group values was misleading because it did not explain that an animal had been censored in one experiment. In the Office Action, the examiner expressed uncertainty about how to interpret the Table 1 data, noting inter alia that the disclosure failed to provide “values for the control group.” In response, Takeda explained that

> Each control value of blood glucose and TG is determined to be 100% and that of “liver weight”, “heart weight” and “number of erythrocyte” is estimated to be zero % from the above numerical expressions. Therefore it is meaningless to show the values of the control. The disclosure of the table ... is sufficient for those skilled in the art to interpret the data.

(Emphasis supplied).

Takeda’s response to the examiner’s inquiry was entirely accurate. It explained why one skilled in the art would

understand all control values to be 100%, and the performance of a compound to be measured against that assumed control value. This explanation helped the examiner to read Table 1; it did not concern the particular experiment in which an animal was censored or even the circumstances more generally in which one animal would be censored in order to obtain a reliable test result. Mylan has not shown that there was any misrepresentation or material omission.

c) ED^{25} data for compound (d)

As noted, the Office Action requested that Takeda provide triglyceride effectiveness data for compounds (c), (d), and (e). These were the only three fields of data not completed in Table 1 as it was originally presented to the PTO. When the supplemental testing done to respond to the Office Action demonstrated no triglyceride-lowering activity in compound (d), Fujita lifted the results from Report A-15-34 and reported a “4" as the ED^{25} value, a number close to the value of “3" reported for pioglitazone. Ciglitazone’s value was “70".

Mylan has not shown that there was any effort to mislead the PTO by reporting a “4" for compound (d). If Takeda had reported that compound (d) had no potency, rather than fairly strong potency, then Mylan may have had grounds to complain. As it was, what Takeda did was utterly inconsistent with any effort to place pioglitazone in a more favorable light than it deserved.

3) Toxicity in Rats

Mylan has argued that Takeda misled the PTO by falsely describing the strain and age of rats that it used to obtain toxicity data.[96] It has failed to show inequitable conduct in either instance.

a) Strains of rats

The studies measuring the potency of compounds were performed in Sprague-Dawley rats, while the toxicology tests were performed in Wistar rats. Takeda represented to the PTO that all of the testing had been performed in Sprague-Dawley rats.[97] Mylan has not shown that this error was material.

Two of the most common strains[98] of laboratory rat used in toxicology studies are Wistar and Sprague-Dawley. Both strains are of healthy animals, and toxicology assays are almost always performed in healthy animals in order to rule out other causes of

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[96] It is not entirely clear if Mylan continues to press these arguments. Mylan did not mention either of these issues in its summation.

[97] The '777 Patent described the experimental process for obtaining data regarding lipid lowering activity and toxicity in rats. The patent represented that the former tests had been conducted with "[m]ale Sprague-Dawley rats" and the latter with "[m]ale and female Sprague-Dawley rats."

[98] A strain is a group of individuals who share a presumed common ancestry and have clear-cut physiological, but not usually morphological, distinctions. Wistar and Sprague-Dawley rats are both outbred strains, meaning that they are maintained as colonies of animals of unidentified genotype. Individual animals from an outbred stock may differ markedly in their genetic characteristics. In contrast, due to cross-breeding of brother-sister pairs in inbred strains over many generations, individuals within an inbred strain are treated as genetic clones.

abnormalities.[99] The Sprague-Dawley strain originated from crosses with Wistar females and remains genetically similar to the Wistar today. Indeed, there are still no genetic markers to differentiate the two strains. Credible expert testimony established at trial that the use of Wistar rats instead of Sprague-Dawley rats did not change the reliability of the conclusions that were presented to the PTO since the same strain was used across the toxicology experiments.[100] There is simply no basis to find that the error was material or made as a result of an intent to mislead.

b) Safety margin analysis

Mylan argues that the value of the safety margin analysis that Takeda developed in response to the Office Action is undercut by the fact that Takeda used Sprague-Dawley rats for its efficacy data, but Wistar rats for the toxicity testing. This argument reflects a fundamental misunderstanding of the testing process. Since the same strain of rat was used as both the control animal and the animal receiving the compound in any given experiment, the efficacy data and the toxicity data were each derived from a scientifically sound experiment. Scientists commonly derive safety margin data using two different animal

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[99] Three dose effectiveness tests were done in normal Sprague-Dawley rats to obtain plasma triglyceride levels. If the levels of treated animals were reduced, that was an indicator of the compound's antidiabetic activity.

[100] For example, when two-week toxicity studies were done in both Wistar and Sprague-Dawley rats for pioglitazone, the results were essentially equivalent.

models. Again, Mylan has not shown that there was any failure to provide the PTO with information material to the examiner.

c) Age of rats

The ‘777 Patent and the Declaration both explain that the toxicity studies in rats were two-week tests done in rats that were “5 weeks old”. In one of the two-week toxicology studies, however, the one in which pioglitazone itself was tested, at the initiation of the study the rats were six weeks of age.[101] Since the results were based on normalized weight calculations and a comparison to control groups of the same age as the test groups, the error in describing the age of the rats was immaterial.

Mylan argued at trial that testing pioglitazone in animals that are one week older gave it an advantage because rats at that age are going through puberty and as more mature and bigger animals will be less susceptible to the toxic effects of the compounds. The credible scientific evidence at trial established that this small difference in age at the point in which the tests began had no effect on the validity of the test results.[102]

Puberty is a process and individual rats generally enter

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[101] Pioglitazone and compound 3894 were tested in rats at least six weeks old. The compounds listed on Table 1 other than pioglitazone were tested in rats five weeks old.

[102] Even though Alphapharm purported to be pursuing an obviousness claim, it chose to cross-examine Takeda’s expert on the issue of the age of the rats, using a series of graphs it prepared based on data drawn from Takeda’s test results. Correctly interpreted, the graphs in fact underscored the expert’s opinion that the one week age difference had no impact whatsoever on the test results.

this process at any time between thirty-five to sixty days, that is, between five to eight and a half weeks. Tests conducted on rats that are from five to seven weeks old and from six to eight weeks old are thus each conducted on rats presumptively undergoing puberty. Using control animals of the same age and normalizing organ weights to body weight, which Takeda did for each test, are sufficient to eliminate any variations of significance among the tests.

B. Omission: Compound 3894

Mylan argues that Takeda had an obligation to disclose to the PTO activity and toxicity data regarding compound 3894, a compound revealed in the prior art, specifically in Sohda II. Compound 3894 is a TZD molecule with a 2-pyridyl ring at the left end, but no substituents on that ring. It is the parent structure for the left hand moeity of the pioglitazone molecule. Mylan argues that if Takeda had revealed that compound 3894 had a comparable activity and toxicity performance to pioglitazone then the PTO "may" have concluded that pioglitazone was not patentable over prior art. Put another way, Mylan argues that Takeda falsely asserted to the PTO that the introduction of an ethyl group to the 2-pyridyl ring produced unexpected results because it knew that pioglitazone is not superior to compound 3894.

In the '777 Patent Takeda made the following statement:

> As is apparent from the experimental results given in Table 1, Compound (I) of this invention is superior to the compounds (a),(c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as

> compared with the compounds (a), (b), (d) and (e). Such an effect as above caused by the introduction of an ethyl group is quite unexpected.
>
> (Emphasis supplied.)

Compound 3894 is toxic. As reflected in Reports A-15-13 and A-15-34, two-week toxicity tests performed in rats demonstrated a statistically significant toxicity to the heart known as cardiomeglia or enlargement of the heart. Mylan has not shown either that Takeda should not have relied on the results reflected in Report A-15-34 in making judgments about the unexpected results achieved through the introduction of an ethyl group, or that the underlying test results on the toxicity of compound 3894 were unreliable.[103]

Mylan points to Takeda documents in which the effects on the heart by compound 3894 were described as "weak" or "mild", as well as Report A-15-13 from February 2004, where this compound was described as one of four compounds that appeared less toxic than the others that had been tested as of that time, and which because of their potency, appeared "much easier to continue further studies including clinical trials." These preliminary views are insufficient to overcome the compelling evidence that as of the Fall 2004, when Report A-15-34 was prepared and Takeda

[103] Mylan first suggested that the statistical significance of the toxicity finding needed to be confirmed through an analysis of variance or ANOVA, with a Dunnett's post-test. Mylan, however, did not perform that test, and when Takeda's expert did, the testing confirmed Takeda's finding of statistical significance. Mylan's expert then speculated that the testing results might be an "artifact". He suggested that the results be confirmed through retesting, but Mylan undertook no such testing.

and Upjohn made their judgments about what toxicity levels would be disqualifying and which compounds warranted further testing, compound 3894 was disqualified because of its toxicity.

As already discussed in connection with the discussion of the issue of obviousness, the closest prior art to pioglitazone was compound (b), not compound 3894.[104] Moreover, it was important to compare pioglitazone to ciglitazone, which had advanced as far as human trials before it had to be abandoned because of toxicity. It was unnecessary for Takeda to present testing data for compound 3894 as well. By presenting the comparison with compound (c), Takeda was presenting data with its methyl-substituted homolog, which was more closely related to pioglitazone in its chemical structure than the unsubstituted compound 3894.

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[104] By the time of its summation, Mylan had abandoned any claim that compound 3894 was the closest prior art. It argued that In re Johnson, 747 F.2d 1456 (Fed. Cir. 1984), requires an applicant for a patent to present information about any relevant prior art, even if it is not the closest prior art. Johnson reaffirms that an applicant must compare the invention to the closest prior art. Id. at 1461. That was done here. Johnson also addresses the duty of comparison where there are two equally close references. Id. That is not an issue presented here.

One Mylan expert had asserted without any analysis that compound 3894 was the closest prior art, but admitted on cross examination to each of the facts on which Takeda's far more impressive and careful expert relied in forming his conclusion that a substituted pyridyl, such as compound (b), is closer structurally to pioglitazone than an unsubstituted pyridyl. To give but one example, the introduction of an alykyl substituent changes the shape of the TZD molecule dramatically, which can have profound effects on the interface between the TZD and the PPAR-gamma molecules.

C. Intent

It is undisputed that Takeda made two misstatements of fact to the PTO. Takeda erred in describing the strain and age of rats used in the toxicity testing. Neither of these errors was material. Mylan has failed to show that Takeda made any other misstatements or failed to provide the PTO with material information. In any event, Mylan has utterly failed to show that Takeda ever acted in bad faith in the prosecution of the '777 Patent.

The evidence of Takeda's good faith is abundant. Takeda's lead scientist for this project was Fujita. As the Chief Scientist of the Biology Research Laboratory, he had ultimate responsibility for the conduct of the screening tests run in 1983 and 1984; he chose the efficacy values for Report A-15-34; and he recommended pioglitazone as one of the twelve compounds from which Takeda and Upjohn should select their candidates in October 1984 for more intensive studies and possible development as a pharmaceutical. He did not include either compound 3894 or any other Table 1 compound among that group of twelve. Fujita has long since retired from Takeda, but he testified at trial. He was an entirely credible witness. Despite extensive cross-examination, he remained a patient, careful witness who worked hard to give precise, accurate answers to every question that he was asked. Although he had no current recollection of many of the details of events from the mid-1980s, his testimony established beyond peradventure that he had used his best

scientific judgment and considerable expertise at that time. He is, in short, an honorable man and distinguished scientist. There is absolutely no evidence that he ever acted with intent to deceive either other scientists at Takeda or Upjohn in preparing Report A-15-34 or the PTO.

Fundamentally, Mylan has never been able to overcome the hurdle presented by the fact that Takeda's work was undertaken in collaboration with Upjohn, and that the Table 1 data were taken directly from Report A-15-34. Even if his character would have permitted him to act other than with complete scientific integrity, Fujita had no motive to use anything other than his best judgment in creating Report A-15-34. He had no way to know what results Upjohn had obtained in testing these same compounds and whether its judgments would agree with his own, and he certainly had no ability to anticipate what data might be important in any future PTO proceedings. As significantly, he had no motive to fabricate data for compounds such as compound (c) that were not even in the prior art.[105] Fujita's only identifiable motive was to choose as wisely as he could the most promising compounds into which Takeda and Upjohn would invest significant resources to determine if they had successfully identified an efficacious, safe compound for use as a

[105] If, for instance, compound (c) had been a better choice for pharmaceutical development than pioglitazone, then Takeda would have had no reason not to select compound (c) for development. It certainly would have been able to show the PTO its unexpected superiority over prior art compound (b) easily, given compound (b)'s extreme toxicity.

pharmaceutical. To place Mylan's argument in stark relief, Mylan would have vehemently complained if Takeda had presented to the PTO any toxicity or efficacy numbers other than those in Reports A-15-13 and A-15-34.

Many of the arguments pressed by Mylan (and Alphapharm) at trial flow from a convoluted theory of a conspiracy by Takeda to obtain patent protection for the 6-ethyl.[106] The 6-ethyl is a homolog of compound (b), which is a prior art compound. This theory suffers from several flaws, including most prominently the fact that when Fujita's department applied internally within Takeda to begin the process of applying for the patent that became the '777 Patent, it sought patent protection for the pioglitazone molecule alone and no other compound. In addition, of course, Takeda has never developed a 6-ethyl compound.

In sum, Mylan has failed to carry its burden of showing either a material misstatement or omission. It has also failed to present any evidence of intent to deceive the PTO.

[106] The '777 Patent claims include not just the pioglitazone molecule, but also each of the ethyls on the 2-pyridine moeity. The ethyl in the sixth position is referred to as the 6-ethyl.

Conclusion

Each defendant having failed to carry its burden at trial, the challenges to the '777 Patent by Alphapharm on the ground of obviousness and by Mylan on the ground of inequitable conduct are denied. Takeda shall submit a proposed judgment.

SO ORDERED:

Dated: New York, New York
February 21, 2006

DENISE COTE
United States District Judge